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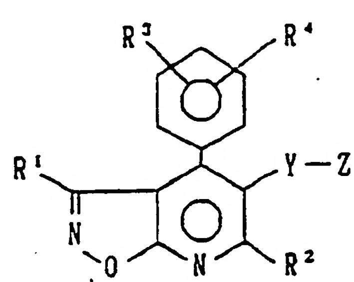
(54) Isoxazolopyridine type mevalonolactones.

(57) The present invention provides a compound of the formula:



(I)

process for their production, pharmaceutical compositions containing them and their pharmaceutical uses, and intermediates useful for their production and processes for the production of such intermediates.

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ISOXAZOLOPYRIDINE TYPE MEVALONOLACTONES

The present invention relates to novel mevalonolactones having a isoxazolopyridine ring, processes for their production, pharmaceutical compoistions containing them and their pharmaceutical uses particularly as hypolipoproteinemic and anti-atherosclerotic agents, and intermediates useful for their production and processes for the production of such intermediates.

Some fermentation metabolic products such as compactin, CS-514, Mevinolin or semi-synthetic derivatives or fully synthetic derivatives thereof are known to be inhibitors against HMG-CoA reductase which is a rate limiting enzyme for cholesterol biosynthesis. (A. Endo J. Med Chem., 28(4) 401 (1985))

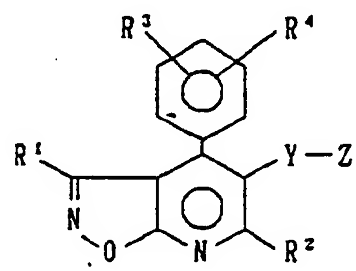
CS-514 and Mevinolin have been clinically proved to be potentially useful anti-hyperlipoproteinemic agents, and they are considered to be effective for curing or preventing diseases of coronary arteriosclerosis or atherosclerosis. (IXth Int. Symp. Drugs Affect. Lipid Metab., 1986, Abstract, p30, p31, p60)

However, with respect to fully synthetic derivatives, particularly hetero aromatic derivatives of inhibitors against HMG-CoA reductase, limited information is disclosed in the following literatures:

WPI ACC No. 84-158675, 86-028274, 86-098816, 86-332070, 87-124519, 87-220987, 88-007781, 88-008460, 88-091798, 88-112505, 88-182950, 88-234828, 88-258359, 88-265052, 88-280597, 88-300969, 89-15672, 89-24911, 89-24913, 89-25270, 89-25474, 89-48221, 89-78429.

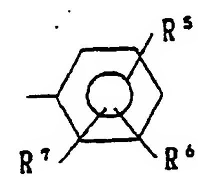
The present inventors have found that mevalonolactone derivatives having a isoxazolopyridine ring, which has not been known, the corresponding dihydroxy carboxylic acids and salts and esters thereof have high inhibitory activities against cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme. The present invention has been accomplished on the basis of this discovery.

The novel mevalonolactone derivatives of the present invention are represented by the following formula I:

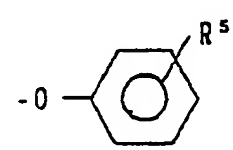


(I)

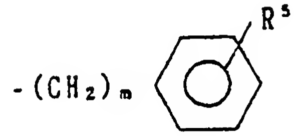
wherein R^1 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, fluoro, chloro, bromo,



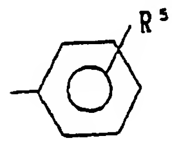
(wherein R^5, R^6 and R^7 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro or bormo), 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, 2- or 5-pyrimidyl,



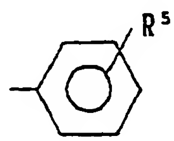
(wherein R^5 is as defined above) or $-NR^8R^9$ (wherein R^8 and R^9 are independently hydrogen, C_{1-4} alkyl or



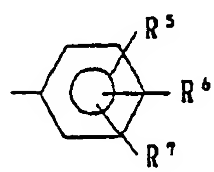
(wherein R^5 is as defined above, and m is 1, 2 or 3) or R^8 and R^9 together form $-(CH_2)_j-$ (wherein j is 3, 4 or 5)); or C_{1-3} alkyl substituted by



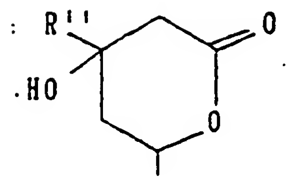
(wherein R^5 is as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-8} alkyl, or α-or β-naphtyl; R^2 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl or

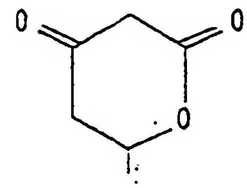


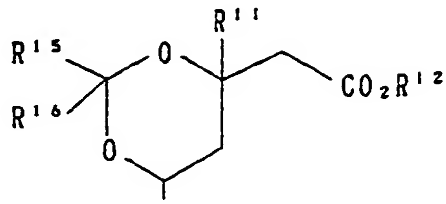
(wherein R^5 is as defined above), or C_{1-3} alkyl substituted by



(wherein R^5, R^6 and R^7 are as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-3} alkyl; R^3 and R^4 are independently hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, t-butoxy, $R^{23}R^{24}N-$ (R^{23} and R^{24} are independently hydrogen or C_{1-3} alkyl), trifluromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $-O(CH_2)_\ell OR^{10}$ (wherein R^{10} is hydrogen, or C_{1-3} alkyl, and ℓ is 1, 2 or 3); or when located at the ortho position to each other, R^3 and R^4 may together form -CH=CH-CH=CH- or methylenedioxy; Y is $-CH_2-$, $-CH_2CH_2-$, -CH=CH-, $-CH_2$-CH=CH-, -CH=CH-CH_2-, $-C(CH_3)$=CH- or -CH=$C(CH_3)$-; and Z is -Q-$CH_2WCH_2-CO_2R^{12}$,







(wherein Q is -C(O)-, -C(OR^{13})$_2$- or -CH(OH)-; W is -C(O)-, -C(OR^{13})$_2$- or -C(R^{11})(OH)-; R^{11} is hydrogen or C_{1-3} alkyl; R^{12} is hydrogen, R^{14} (wherein R^{14} is alkyl moiety of chemically or physiologically hydrolyzable alkyl ester or M (wherein M is $NHR^{17}R^{18}R^{19}$ (wherein R^{17}, R^{18} and R^{19} are independently hydrogen or C_{1-4} alkyl), sodium, potassium or 1/2 calcium); two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form -$(CH_2)_2$- or -$(CH_2)_3$-; and R^{15} and R^{16} are independently hydrogen or C_{1-3}alkyl; or R^{15} and R^{16} together form -$(CH_2)_2$- or -$(CH_2)_3$-).

Various substituents in the formula I will be described in detail with reference to specific examples. However, it should be understood that the present invention is by no means restricted by such specific examples.

C_{1-8} alkyl for R^1, R^2, R^3 and R^4 includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, 1,2 dimethylpentyl, n-hexyl, n-heptyl and n-octyl.

C_{1-4} alkyl for R^5, R^6, R^7, R^8, R^9, R^{17}, R^{18} and R^{19} includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl.

C_{1-3} alkyl for R^{10} R^{11}, R^{15}, R^{16}, R^{23} and R^{24} includes, for example, methyl, ethyl, n-propyl and i-propyl.

When R^{12} is alkyl, $R^{1}4$ includes methyl, ethyl, n-propyl, i-propyl, c-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl (amyl), i-pentyl and n-hexyl.

C_{1-6} alkyl for R^{13} includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, n-pentyl and n-hexyl.

C_{3-7} cycloalkyl for R^1, R^2, R^3, R^4, R^5, R^6 and R^7 includes, for example, cyclopropyl, 1-methylcyclopropyl, 2-methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl and cycloheptyl.

C_{1-6} alkoxy for R^1 includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy, n-pentyloxy and n-hexyloxy.

C_{1-3} alkoxy for R^3, R^4, R^5, R^6 and R^7 includes, for example, methoxy, ethoxy, n-propoxy and i-propoxy.

C_{1-6} alkylthio for R^1 includes, for example, methylthio, ethylthio, i-propylthio and n-hexylthio.

C_{2-6} alkenyl for R^1 and R^2 includes, for example, vinyl, 1-methylvinyl, 1-propenyl, allyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-butenyl, 1-ethylvinyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl and 1-methyl-1-pentenyl.

C_{5-7} cycloalkenyl for R^2 includes, for example, 2-cyclopentenyl, 2-cyclohexenyl, 2-cycloheptenyl and 4-methyl-2-cyclohexenyl.

M is a metal capable of forming a pharmaceutically acceptable salt and includes, for example, sodium, potassium and 1/2 calcium. CO_2M includes, for example, -CO_2NH_4 and -CO_2H•(primary to tertiary lower alkylamine, for example, triethylamine).

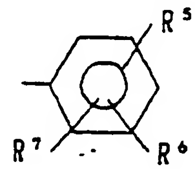
Further, thes compounds may have at least one or two asymmetric carbon atoms and may have at least two to four optical isomers. The compounds of the formula I include all of these optical isomers and all of the mixtures thereof.

Among compounds having carboxylic acid moieties falling outside the definition of -CO_2R^{12} of th carboxylic acid moiety of substitutent Z of the compounds of the present invention, those which undergo physi logical hydrolysis, after intake, to produce the corresponding carboxylic acids (compounds wherein the -CO_2R^{12} moiety is -CO_2H) are equivalent to the compounds of the present invention.

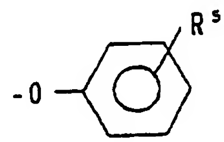
Now, preferred substitutents of the compounds of the present invention will be described.

In the following preferred, more preferred, still further preferred and most preferred examples, the numerals for the positions of the substituents indicate the positions on the isoxazolopyridine ring.

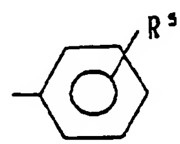
Preferred compound (1) of the formula I is a compound wherein R^1 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, fluoro, chloro, bromo,



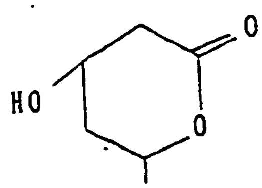
(wherein R^5, R^6 and R^7 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro or bromo), 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, 2- or 5-pyrimidyl or



(wherein R^5 is as defined above), or C_{1-3} alkyl substituted by

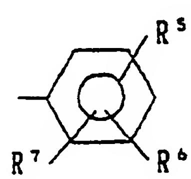


(wherein R^5 is as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-8} alkyl, or α-or β-naphthyl; R^2 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl; R^3 and R^4 are independently hydrogen, C_{1-8} alkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, t-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $-O(CH_2)_{\ell}OR^{10}$ (wherein R^{10} is hydrogen, or C_{1-3} alkyl, and ℓ is 1, 2 or 3); or when located at the ortho position to each other, R^3 and R^4 may together form methylenedioxy; Y is $-CH_2CH_2-$ or $-CH=CH-$; and Z is $-Q-CH_2WCH_2-CO_2R^{12}$,

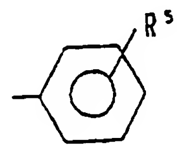


(wherein Q is -C(O)- or -CH(OH)-; W is -C(O)- or -C(OH)-; and R^{12} is as defined in Claim 1.

More preferred compound (2) of the formula I is a compound wherein R^1 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl,

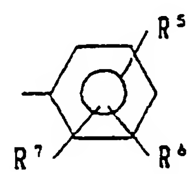


(wherein R^5, R^6 and R^7 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro or bromo), 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, or 2- or 5-pyrimidyl; or C_{1-3} alkyl substituted by

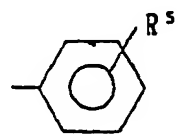


(wherein R^5 is as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-8} alkyl, or α-or β-naphthyl; R^2 is primary or secondary C_{1-4} alkyl or C_{3-6} cycloalkyl; R^3 and R^4 are as defined with respect to the compound (1) and located at the 3- and 4-position; Y is -CH_2CH_2- or (E)-CH=CH-; and Z is as defined with respect to the compound (1).

Still further preferred compound (3) of the formula I is a compound wherein R^1 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl,
C_{3-7} cycloalkyl,



(wherein R^5, R^6 and R^7 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro or bromo); or C_{1-3} alkyl substituted by



(wherein R^5 ia as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-8} alkyl; R^2 is ethyl, n-propyl, i-propyl or cyclopropyl; R^3 and R^4 are independently hydrogen, C_{1-8} alkyl, fluoro, chloro or bromo, and they are located at the 3- and 4-position; and Y and Z are as defined with respect to the compound (2).

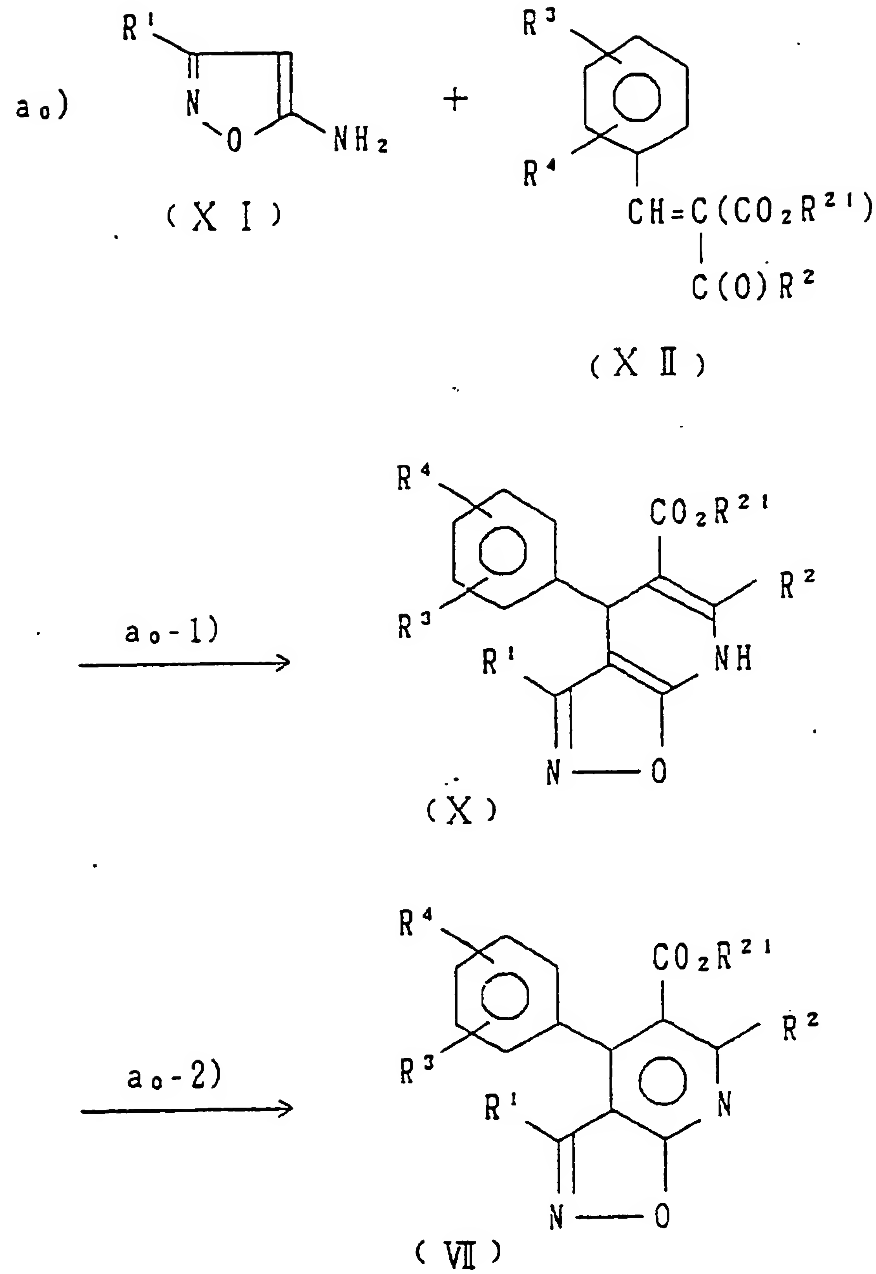
The most preferred compound (4) is a compound wherein R^1 is hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl, t-butyl, n-hexyl, n-octyl, vinyl, isopropenyl, cyclopropyl, cyclohexyl, phenyl, 2-toluyl, 3-toluyl, 4-toluyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethylphenyl, 3,4-dimethoxyphenyl, benzyl, α-methylbenzyl, 4-chlorobenzyl or 4-methoxybenzyl; R^2 is i-propyl or cyclopropyl; when R^4 is hydrogen, R^3 is hydrogen, 3-methyl, 4-methyl, 3-chloro, 4-chloro, 3-fluoro or 4-fluoro; or R^3 and R^4 together form 3-methyl-4-chloro, 3,5-dichloro, 3,5-difluoro, 3,5-dimethyl or 3-methyl-4-fluoro; and Y and Z are as defined with respect to the compoud (2).

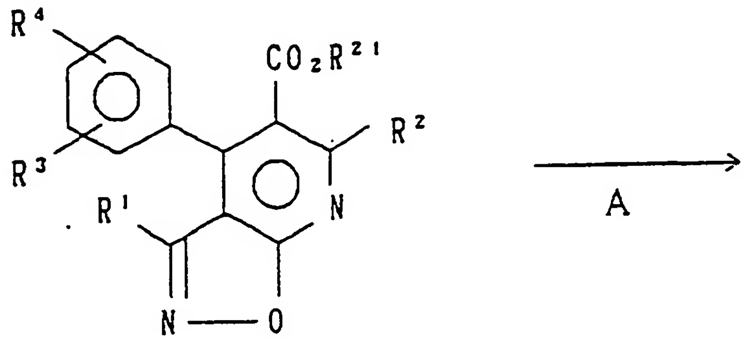
Now, particularly preferred specific compounds of the present invention will be presented.

(a) (E)-7-[4′-(4″-fluorophenyl)-3′-methyl-6′-(1″-methylethyl)isoxazolo[5,4-b]pyridin-5′-yl]-3,5-dihydroxyhept-6-enoic acid, a sodium salt, methyl ester, ethyl ester, n-propyl ester or i-propyl ester of the carboxylic acid, or a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position

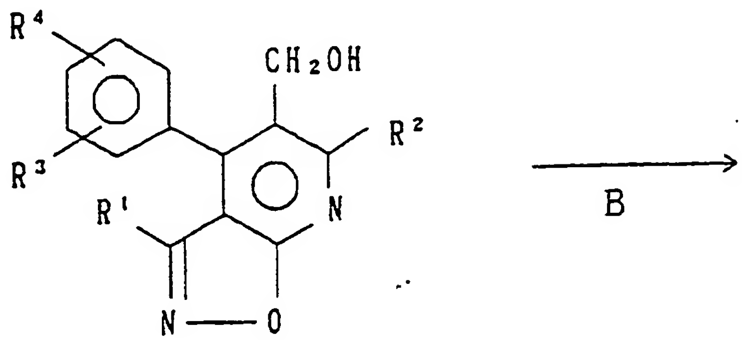
(b) (E)-7-[4′-(4″-fluorophenyl)-6′-(1″-methylethyl)-3′-phenylisoxazolo[5,4-b]pyridin-5′-yl]-3,5-dihydroxyhept-6-enoic acid, a sodium salt, methyl ester, ethyl ester, n-propyl ester or i-propyl ester of th carboxylic acid, or a lactone formed by th condensation of the carboxylic acid with the hydroxy at th 5-position

The mevalonolactones of the formula I can be prepared by the following reaction scheme.

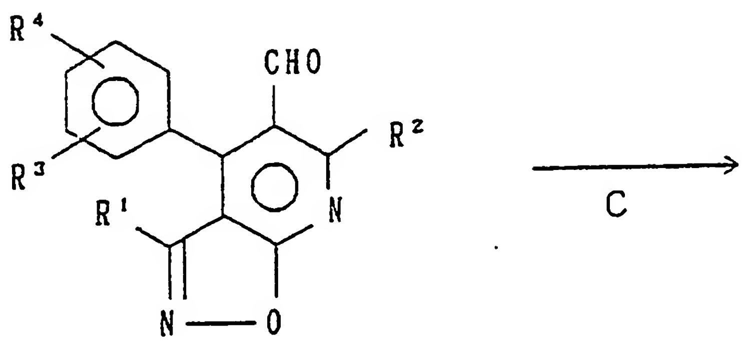

a₀)
(XI)
(XII)
a₀-1)
(X)
a₀-2)
(VII)


R⁴
CO₂R²¹
R²
R³
R¹
N
N
O
A

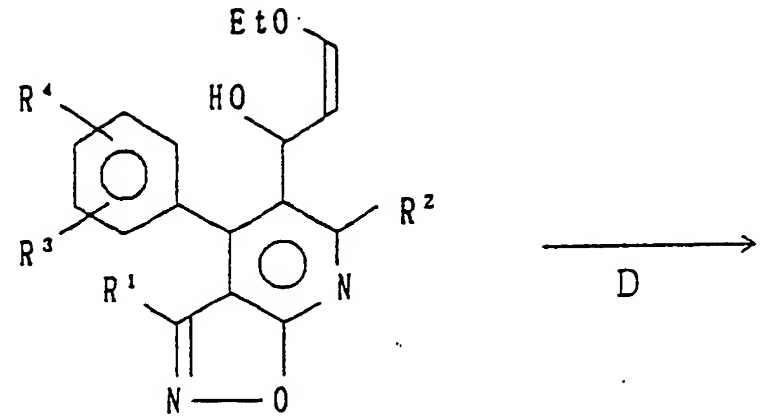
(VII)


R⁴
CH₂OH
R²
R³
R¹
N
N
O
B

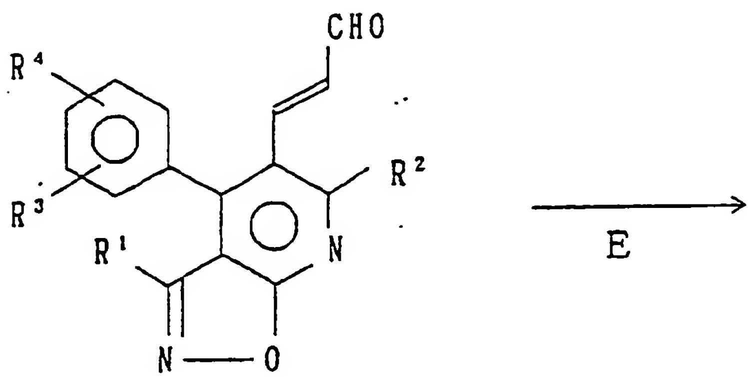
(VI)


R⁴
CHO
R²
R³
R¹
N
N
O
C

(V)



(IV)



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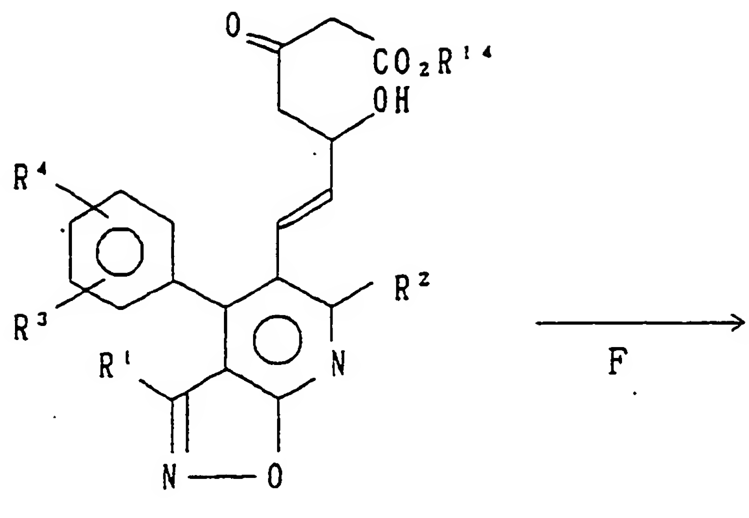
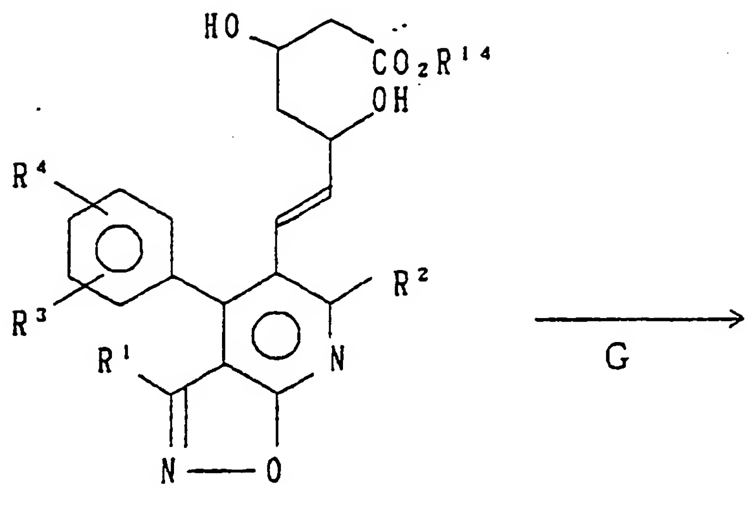
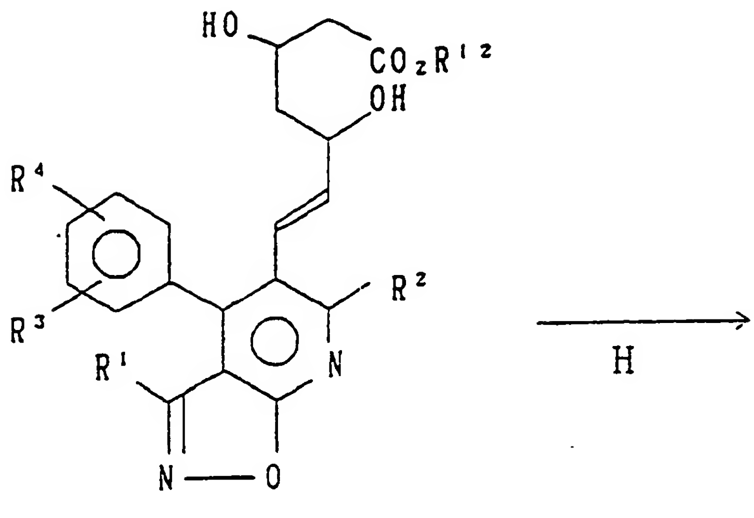


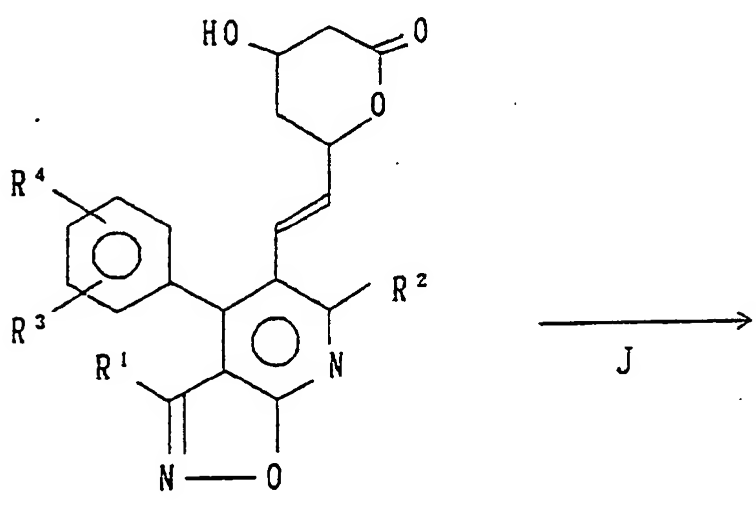
(II)



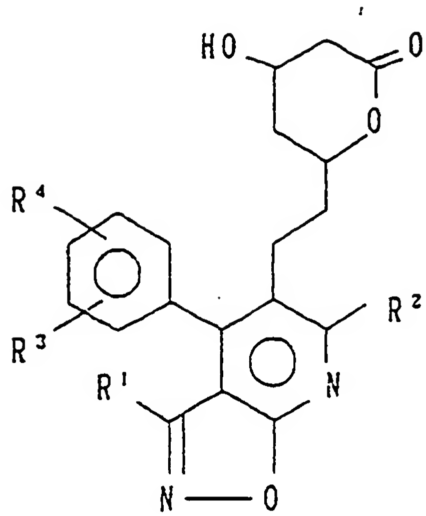
(I − 1)



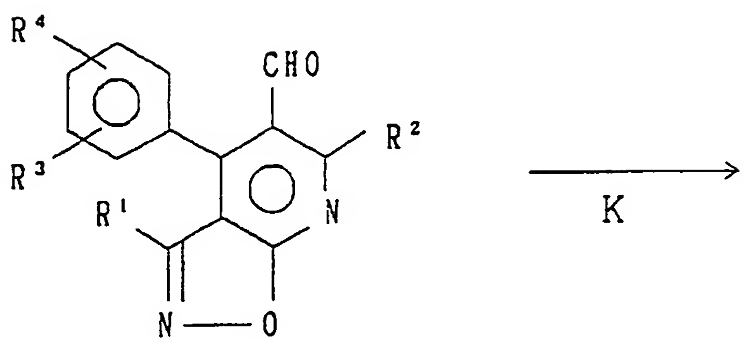
(I − 2) (R^{12} = H)
(I − 5) (R^{12} = Na)



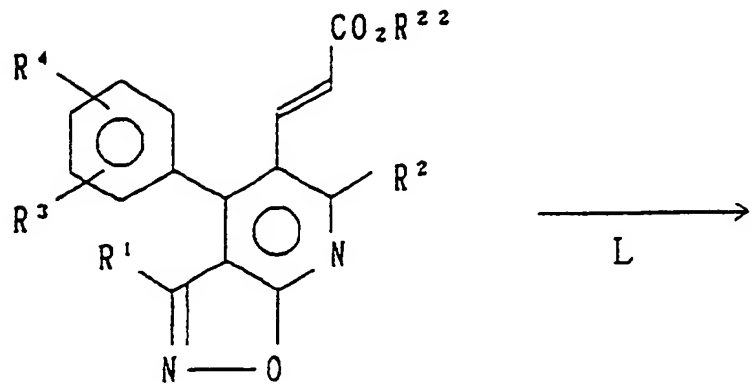
(I − 3)



(I − 4)



(V)



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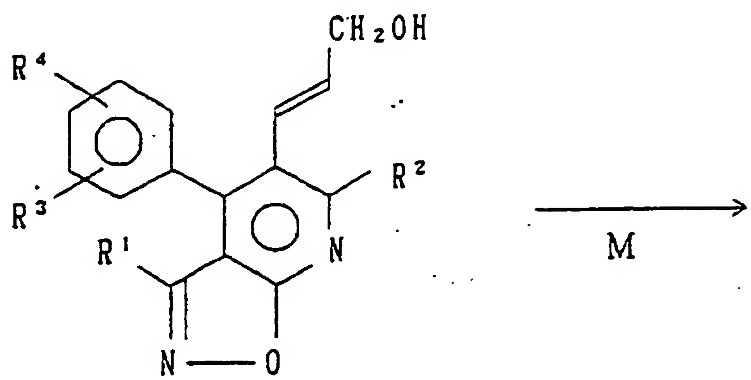

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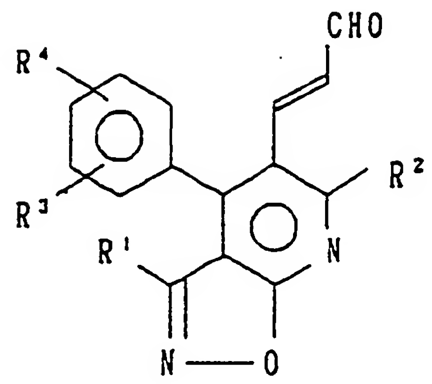

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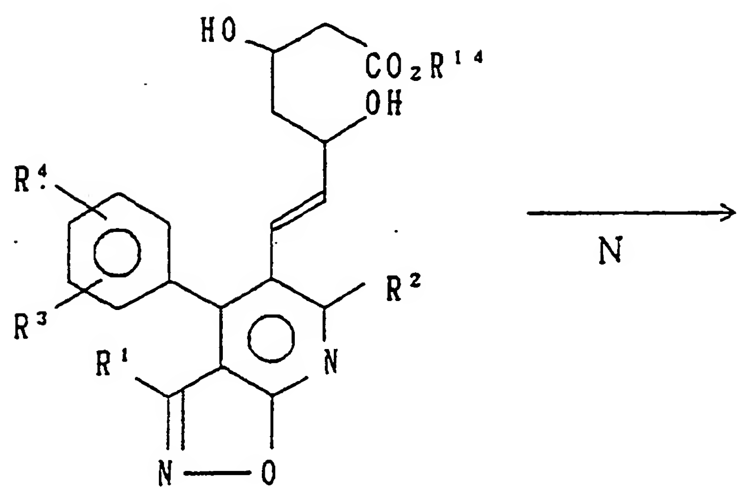

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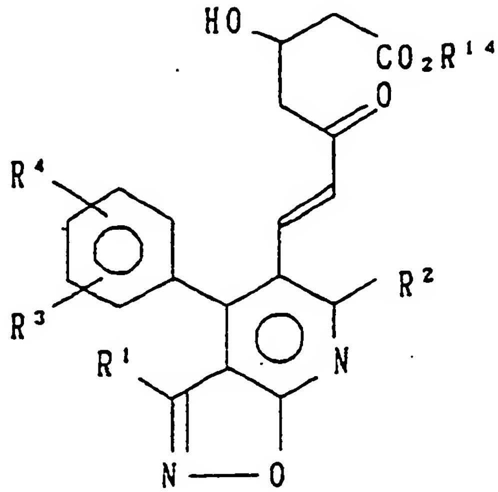
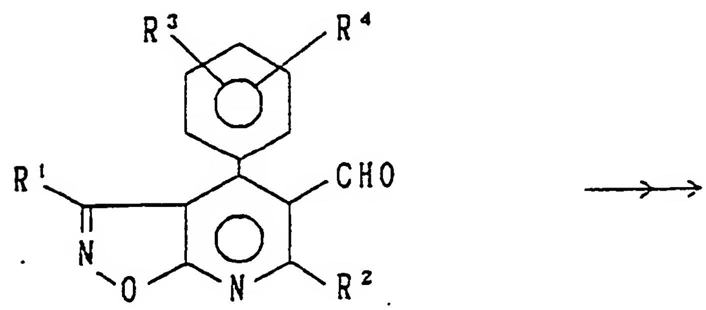


(I − 6)



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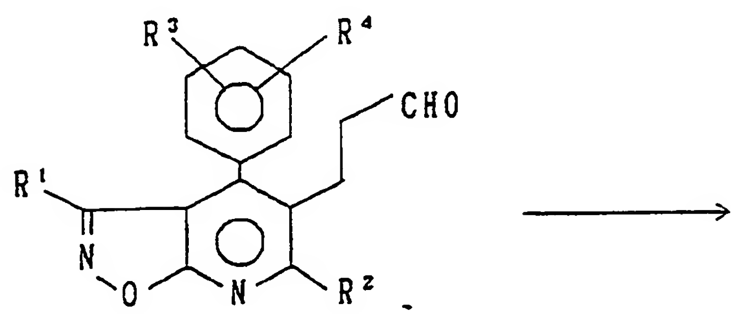

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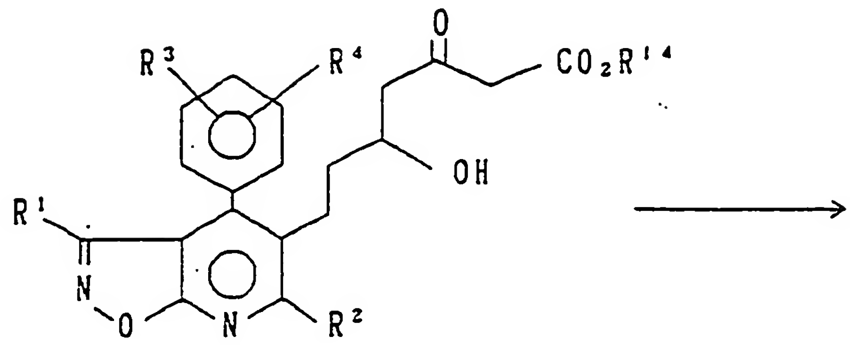

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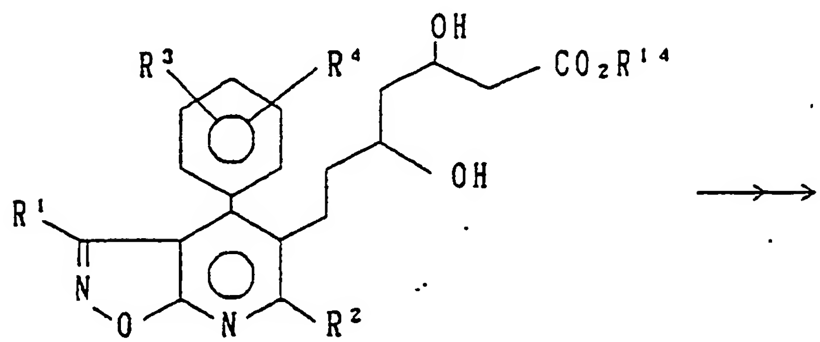

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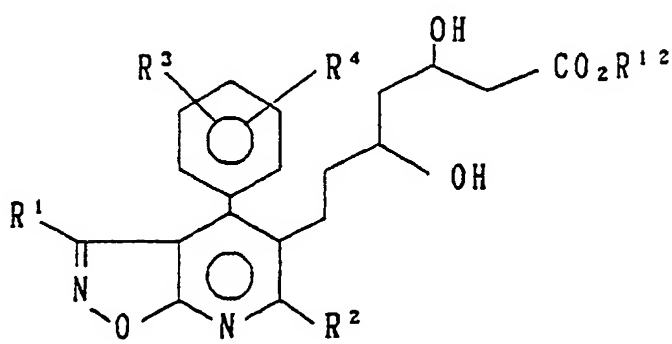
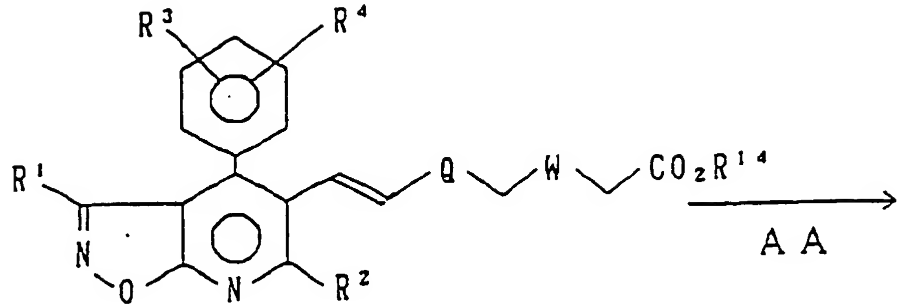
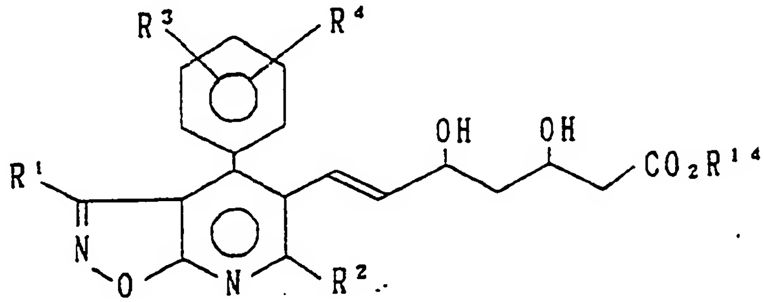


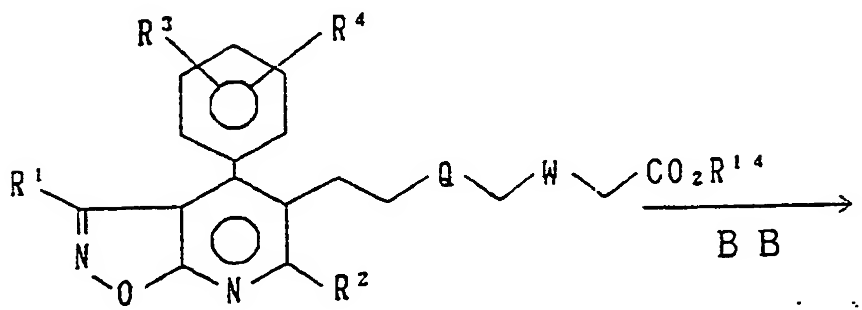
I - 8 ((R^{12} = H))
I - 9 ((R^{12} = Na))



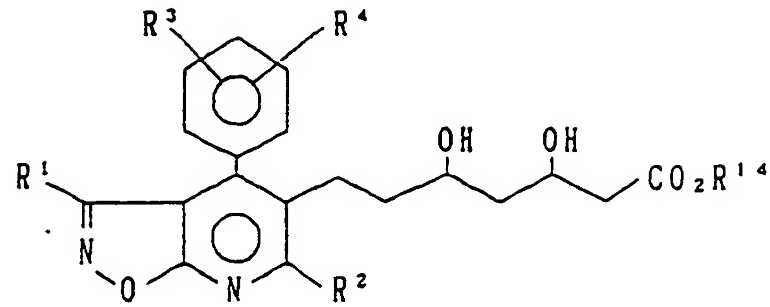
(I - 6) (Q = -C(O)-、 W = -CH(OH)-)
(XV) (Q = -C(O)-、 W = -C(O)-)



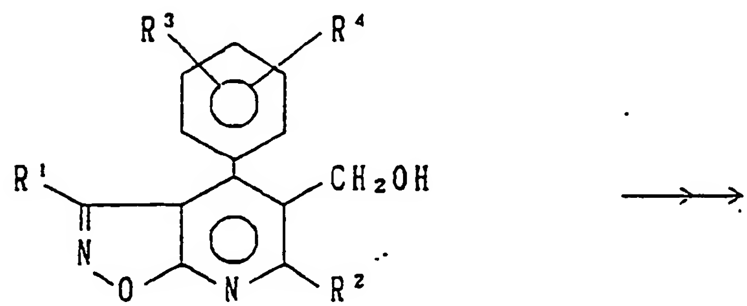
(I - 1)



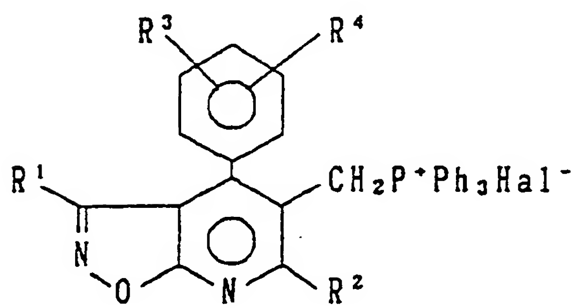
(XVI) (Q = -C(O)-、 W = -CH(OH)-)
(XVII) (Q = -C(O)-、 W = -C(O)-)



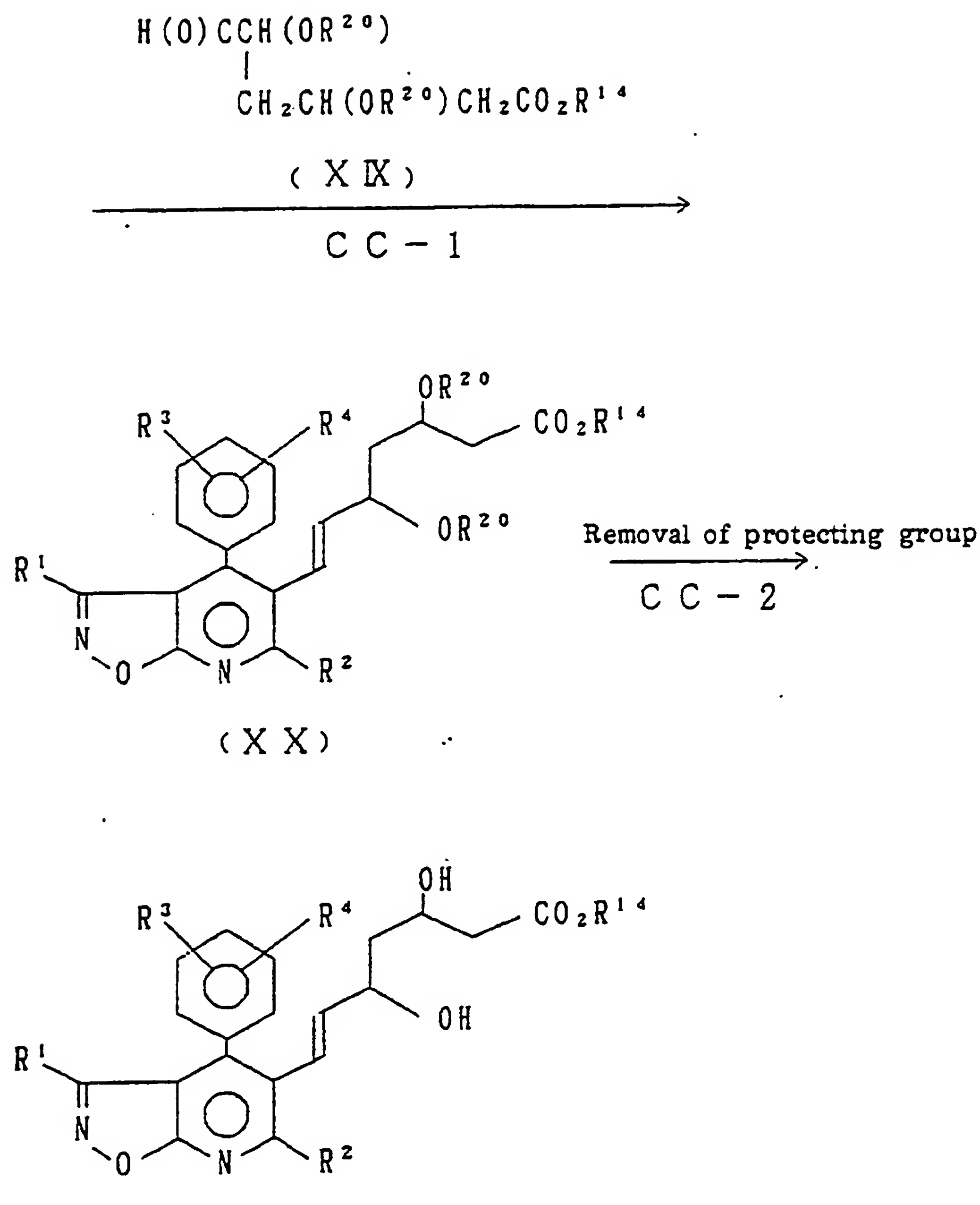
(I − 7)



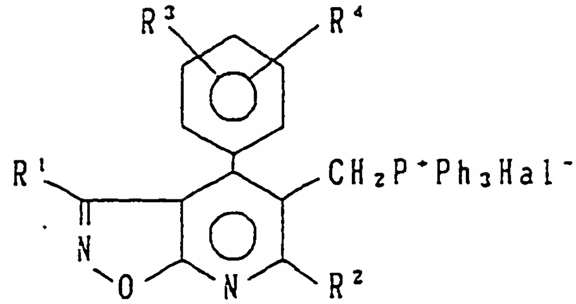
(VI)



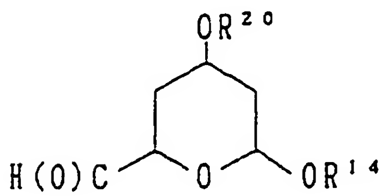
(XVIII)


H(O)CCH(OR20)
CH2CH(OR20)CH2CO2R14
(XIX)
CC-1
OR20
CO2R14
R3
R4
OR20
R1
N
O
N
R2
(XX)
Removal of protecting group
CC-2
OH
CO2R14
R3
R4
OH
R1
N
O
N
R2

(I - 1)

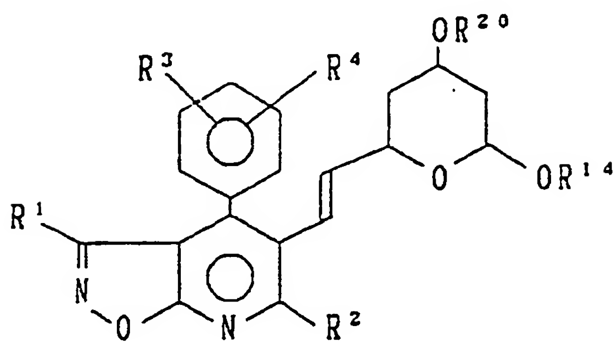


(XVIII)



(XXI)

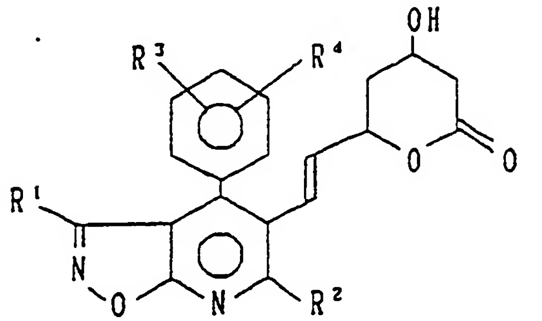
DD-1



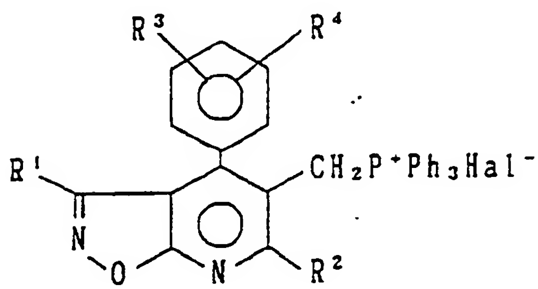
(XXII)

① hydrolysis ② Oxidation ③ Removal of protecting group

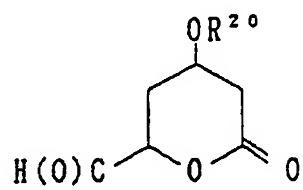
$\xrightarrow[\text{DD-2}]{\text{(1) hydrolysis (2) Oxidation}}$ $\xrightarrow[\text{DD-3}]{\text{(3) Removal of protecting group}}$



(I − 3)

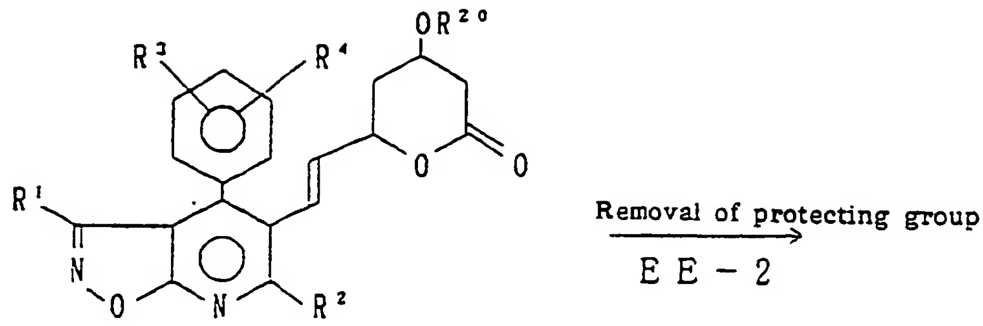


(XVIII)

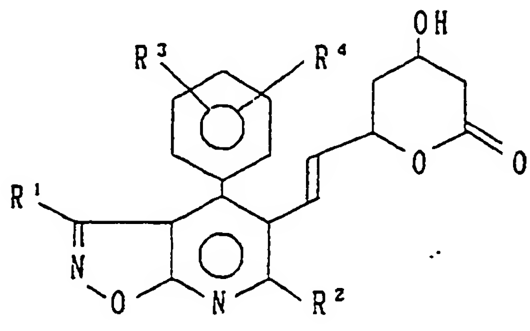


(XXIII)

$\xrightarrow[\text{EE-1}]{}$



(XXIV)



(I-3)

In the above reaction scheme, R^1, R^2, R^3, R^4 and R^{14} are as defined above with respect to the formula I, and R^{21} and R^{22} independently represent C_{1-4} lower alkyl such as methyl, ethyl, n-propyl, i-propyl or n-butyl.

The compound of the formula VII can be prepared by oxidizing the compound of the formula X obtained by reacting the compound of the formula XI with the compound of the formula XII (Japanese Unexamined Patent Publication No. 152386/1984).

Step A represents a reduction reaction of the ester to a primary alcohol. Such reduction reaction can be conducted by using various metal hydrides, preferably diisobutylaluminium hydride, in a solvent such as tetrahydrofuran, toluene or methylene chloride at a temperature of from -20 to 20° C, preferably from -10 to 10° C.

Step B represents an oxidation reaction of the primary alcohol to an aldehyde, which can be conducted by using various oxidizing agents. Preferably, the reaction can be conducted by using pyridinium chlorochromate in methylene chloride at a temperature of from 0 to 25° C, or by using oxalyl chloride, dimethyl sulfoxide and a tertiary amine such as triethylamine (Swern oxidation), or by using a sulfur trioxide pyridine complex.

Step C represents a synthesis of a 3-ethoxy-1-hydroxy-2-propene derivative, which can be prepared by reacting a compound V to a lithium compound which has been preliminarily formed by treating cis-1-ethoxy-2-(tri-n-butylstannyl)ethylene with butyl lithium in tetrahydrofuran.

As the reaction temperature, it is preferred to employ a low temperature at a level of from -60 to -78° C.

Step D represents a synthesis of an enal by acidic hydrolysis. As the acid catalyst, it is preferred to employ p-toluenesulfonic acid, hydrochloric acid or sulfuric acid, and the reaction may be conducted in a solvent mixture of water and tetrahydrofuran or ethanol at a temperature of from 10 to 25° C. The 3-ethoxy-1-hydroxy-2-propene derivative obtained in Step C can be used in Step D without purification i.e. by simply removing tetra-n-butyl tin formed simultaneously.

Step E represents a double anion addition reaction between the enal III and an acetoacetate. Such

addition reaction is preferably conducted by using sodium hydride and n-butyl lithium as the base in tetrahydrofuran at a temperature of from -80 to 0° C, preferably from -30 to -10° C.

Step F r presents a reduction reaction of the ketocarboxylat of the formula II, by various reducing agents. This reaction comprises reduction of carbonyl by e.g. sodium borohydride, sodium cyanoborohydride, zinc borohydride, disiamylborane, diborane, t-butylaminoborane, pyridine-borane complex, dicyclohexylborane, thexylborane, 9- borabicyclo[3.3.1]nonane, diisopinocamphenyl borane or lithium tri-sec-butyl borohydride to the corresponding dihydroxycarboxylate of the formula I-1.

This reaction can be conducted in a solvent selected from hydrocarbons, halogenated hydrocarbons, C_{1-4} alcohols, ethers and solvent mixtures thereof, at a temperature of from -100 to 50° C, preferably from -78 to 30° C.

Further, as described in J. Amer. Chem. Soc., 105, 593 (1983), a trialkylborane such as tri-n-butylborane or triethylborane and sodium borohydride are used at a low temperature. Further, as described in Tetrahedron Letters, 28, 155 (1987), the erythro form having biologically superior activities can advantageously be obtained by using an alkoxydialkylborane such as methoxydiethylborane or ethoxydiethylborane and sodium borohydride.

This reaction can be conducted by using a solvent mixture of C_{1-4} alcohol and tetrahydrofuran at a temperature of from -80 to -50° C, preferably from -72 to -68° C.

Step G is a step for hydrolyzing the ester. The hydrolysis can be conducted by using an equimolar amount of a base, preferably potassium hydroxide or sodium hydroxide, in a solvent mixture of water and methanol or ethanol at a temperature of from 10 to 25° C. The free acid hereby obtained may be converted to a salt with a suitable base.

Step H is a step for forming a mevalonolactone by the dehydration reaction of the free hydroxy acid I-2. The dehydration reaction can be conducted in benzene or toluene under reflux while removing the resulting water or by adding a suitable dehydrating agent such as molecular sieve.

Further, the dehydration reaction may be conducted in dry methylene chloride by using a lactone-forming agent such as carbodiimide, preferably a water soluble carbodiimide such as N-cyclohexyl-N′-[2′-(methylmorpholinium)ethyl]carbodiimide p-toluene sulfonate at a temperature of from 10 to 35° C, preferably from 20 to 25° C.

Step J represnts a reaction for hydrogenating the double bond connecting the mevalonolactone moiety and the isoxazolopyridine ring. This hydrogenation reaction can be conducted by using a catalytic amount of palladium-carbon or rhodium-carbon in a solvent such as methanol, ethanol, tetrahydrofuran or acetonitrile at a temperature of from 0 to 50° C, preferably from 10 to 25° C.

Step K represents a reaction for the synthesis of an α,β-unsaturated carboxylic acid ester, whereby a transform α,β-unsaturated carboxylic acid ester can be obtained by a so-called Horner-Wittig reaction by using an alkoxycarbonylmethyl phosphonate. The reaction is conducted by using sodium hydride or potassium t-butoxide as the base in dry tetrahydrofuran at a temperature of from -30 to 0° C, preferably from -20 to -15° C.

Step L represents a reduction reaction of the α,β-unsaturated carboxylic acid ester to an allyl alcohol. This reduction reaction can be conducted by using various metal hydrides, preferably diisobutylaluminum hydride, in a solvent such as dry tetrahydrofuran or toluene at a temperature of from -10 to 10° C, preferably from -10 to 0° C.

Step M represents an oxidation reaction of the allyl alcohol to an enal. This oxidation reaction can be conducted by using various oxidizing agents, particularly activated manganese dioxide, in a solvent such as tetrahydrofuran, acetone, ethyl ether or ethyl acetate at a temperature of from 0 to 100° C, preferably from 15 to 50° C, or in accordance with so-called Swern oxidation by using oxalyl chloride, dimethylsulfoxide and a tertiary amine such as triethylamine.

Step N represents a reaction for the synthesis of an α,β-unsaturated ketone by the selective oxidation of the dihydroxy carboxylic acid ester. This reaction can be conducted by using activated manganese dioxide in a solvent such as ethyl ether, tetrahydrofuran, benzene or toluene at a temperature of from 20 to 80° C, preferably from 40 to 80° C.

Further, the compound of the formula I-6 can be prepared from the aldehyde of the formula V by Wadsworth- Emmons coupling reaction (J. Amer. Chem. Soc., 107, 3731 (1985)). It can also be prepared from the enal of the formula III (Tetrahedron Letters, 26, 2951 (1985)).

Further, the compound of the formula I-7 can be prepared by adding a double anion of an acetoacetate to the aldehyde of the formula XIII prepared by the continuous Wittig reaction (WO-8402131) from the aldehyde of th formula V in the same manner as in Step E, to obtain the ketocarbaoxylate of the formula XIV, and reducing the carbonyl group in the same manner as in Step F.

Step AA represents a reduction reaction of the ketocarboxylat of the formula I-6 or XV by various

reducing agents. This reaction comprises reduction of carbonyl by e.g. sodium borohydride, sodium cyanoborohydride, zinc borohydride, disiamylborane, diboran , t-butylaminoborane, pyridine-borane complex, dicyclohexylborane, thexylborane, 9-borabicyclo[3.3.1]nonane, diisopinocamphenyl borane or lithium tri-sec-butyl borohydride to the corresponding dihydroxycarboxylate of the formula I-1.

This reaction can be conducted in a solvent selected from hydrocarbons, halogenated hydrocarbons, C_{1-4} alcohols, ethers and solvent mixtures thereof, at a temperature of from -100 to 50°C, preferably from -78 to 30°C.

Further, as described in J. Amer. Chem. Soc., 105, 593 (1983), a trialkylborane such as tri-n-butylborane or triethylborane and sodium borohydride are used at a low temperature. Further, as described in Tetrahedron Letters, 28, 155 (1987), the erythro form having biologically superior activities can advantageously be obtained by using an alkoxydialkylborane such as methoxydiethylborane or ethoxydiethylborane and sodium borohydride.

This reaction can be conducted by using a solvent mixture of C_{1-4} alcohol and tetrahydrofuran at a temperature of from -80 to -50°C, preferably from -72 to -68°C.

Step BB represents a reaction of reducing the carbonyl group of the ketocarboxylate of the formula XVI or XVII by using various reducing agent to obtain the corresponding dihydroxycarboxylate of the formula I-7. This reaction can be conducted in the same manner as in Step AA.

Substituents R^1, R^2, R^3 and R^4 in from the compound of the formula VI which is an intermediate material of the phosphonium compound of the formula XVIII used in Steps CC-1, DD-1, EE-1 and the like, to the compounds of the formula XX, XXII and XXIV, are those defined with respect to the formula I excluding substituents having hydroxyl, amino and monoalkylamino.

Steps CC-1 and CC-2 comprise reacting the compound of the formula XIX with the compound of the formula XIII (wherein Hal is chlorine, bromine or iodine) by Wittig reaction to obtain the compound of the formula XX, (Step CC-1), followed by hydrolysis of the hydroxyl-protecting group (R^{20}) of the compound XX in the presence of a catalyst to obtain the compound of the formual I-1 (Step CC-2).

The phosphonium compound of the formula XVIII can be obtained by halogenating the hydroxyl group of the hydroxymethyl at the 5-position of the isoxazolopyridine ring of the compound of the formula VI by a usual method, and then, reacting triphenylphosphine therewith.

The reactions of Steps CC-1 and CC-2 can be conducted in accordance with the method disclosed in Tetrahedron Letters, 25, 2435 (1984), US Patent 4,650,890, EP 0 244 364, etc.

Wittig reaction can be conducted in a dry inert solvent. As the inert solvent, an aliphatic hydrocarbon, toluene or an ether type solvent may be mentioned. Preferred is the ether type solvent, such as diethyl ether, 1,2-diethoxyethane, 1,2-dimethoxyethane or tetrahydrofuran.

Wittig reaction can be conducted in a usual manner. A strong base is added to a solution of the phosphonium compound of the formula XVIII within a temperature range which does not affect the substituents of the phoshonium compound, to form the corresponding ylide compound, and then, the aldehyde of the formula XIX is added to the solution to form the desired compound.

As examples of the strong base, sodium hydride and n-butyl lithium may be mentioned, and preferred is n-butyl lithium.

The temperature upon the addition of the strong base is from -40 to 25°C, and the temperature upon the addition of the aldehyde is -35 to 30°C.

The hydroxyl-protecting group (R^{20}) of the compound of the formula XIX, XX, XXI, XXII, XXIII or XXIV is tri-substituted silyl, preferably diphenyl-t-butylsilyl, which is usually used as a hydroxyl-protecting group. Preferred is a protecting group which can be removed without decomposition of the ester or the lactone. The solvent used for the removal of the protecting group is an inert solvent such as tetrahydrofuran or methanol. The catalyst used for the removal of the protecting group is one commonly used for the reaction for removal of silyl. For example, a mixture of acetic acid and tetrabutylammonium fluoride in tetrahydrofuran, or hydrochloride in methanol, may be mentioned.

The reaction temperature for the removal of the protecting group is from 20 to 60°C, preferably from 20 to 30°C.

When there are hydroxyl-protecting groups other than R^{20} at the time of the removal of the protecting group, such protecting groups may be removed to form hydroxyls.

Steps DD-1 to DD-3 represent Wittig reaction of the compound of the formula XVIII with the compound of the formula XXI (Step DD-1), followed by hydrolysis of the acetal to form the hemiacetal, by oxidation of the hemiacetal to form the lactone (Step DD-2), and then, by removal of the hydroxyl-protecting group (R^{20}) (Step DD-3).

The hydroxyl-protecting group (R^{20}) is as defined in Steps CC-1 and CC-2.

The reaction condition for Step DD-1 may be the same as in the method of Step CC-1.

Step DD-2 represents (1) th hydrolysis and (2) th oxidation. The hydrolysis can be conducted in a solvent mixture such as 10% HCl in tetrahydrofuran or acetic acid/water/tetrahydrofuran, preferably acetic acid/water/tetrahydroruran.

Th reaction temperature is from 10 to 100° C, preferably from 20 to 60° C.

The oxidation of the hemiacetal formed by the hydrolysis can be conducted under a mild condition. The reaction condition varies depending upon the type of the oxidizing agent used.

When the oxidizing agent is pyridinium chlorochromate, the reaction temperature is from 20 to 30° C, and the solvent used is halogenated hydrocarbons, preferably methylene chloride.

Swern oxidation is conducted by using a mixture system of oxalyl chloride/dimethylsulfoxide/triethylamine as the oxidizing agent, the reaction temperature is from -60 to -40° C, and the solvent used is a halogenated hydrocarbon, preferaby methylene chloride.

When the oxidizing agent is N-methylmorpholinoxide and dichloro-tris((phenyl)$_3$P)-ruthenium II, the reaction temperature is from 0 to 40° C, preferably from 20 to 30° C, and the solvent is dry dimethylformamide or acetone.

When the oxidizing agent is $AgCO_3$ on Celite, the reaction temperature is from 0° C to the boiling point of the reaction solution, preferably at most 150° C, and the solvent is benzene, toluene, xylene, etc.

The reaction condition for the removal of the protecting group in Step DD-3 may be the same as in the method of Step CC-2.

Steps EE-1 and EE-2 represent Wittig reaction of the compound of the formula XVIII with the compound of the formula XXIII (Step EE-1) followed by removal of the hydroxyl-protecting group (R^{20}) (Step EE-2).

The hydroxyl-protecting group (R^{20}) is as defined in Steps CC-1 and CC-2.

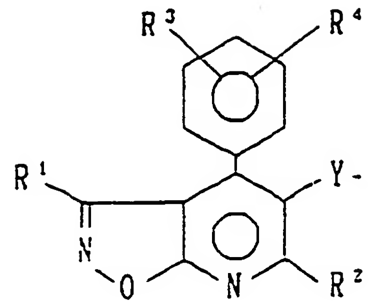
The reaction condition for the Step EE-1 may be the same as in the method of Step CC-1.

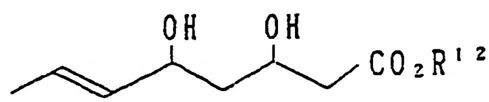
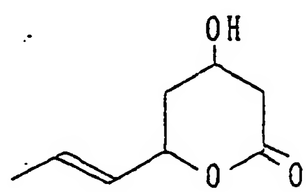
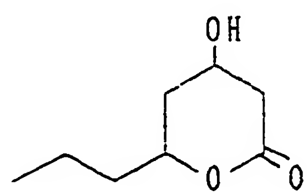
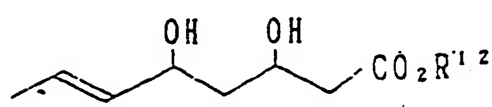
The reaction condition for removing the protecting group in Step EE-2 may be the same as in the method of Step CC-2.

The compounds of the formulas I-1, I-2, I-3, I-4, I- 5, I-6, I-7, I-8, I-9, II, XIV and XVI shown in Table 1, are typical examples of the compounds of the present invention.

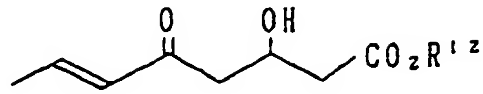
In Table 1, and in the following description, n-means mormal, i- means iso, sec- means secondary, t-means tertiary and c- means cyclo. Likewise, Me means methyl, Et means ethyl, Pr means propyl, Bu means butyl, Pent means pentyl, Hex means hexyl and Ph means phenyl.

Table 1

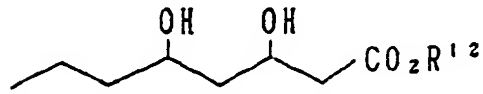


Compound	$-Y-Z$
(I - 1) (R^{12}=Et)	
(I - 2) (R^{12}=H)	same as above
(I - 3)	
(I - 4)	
(I - 5) (R^{12}=Na)	

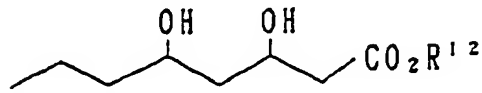
(I − 6) (R^{12}=Et)



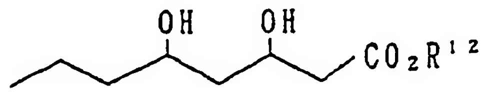
(I − 7) (R^{12}=Et)



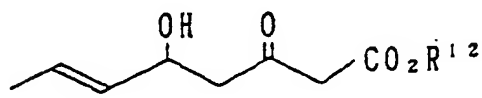
(I − 8) (R^{12}=H)



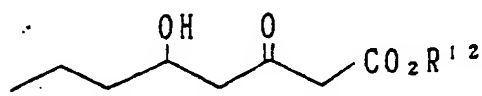
(I − 9) (R^{12}=Na)



(II) (R^{12}=Et)



(XIV) (R^{12}=Et)



(XVI) (R^{12}=Et)

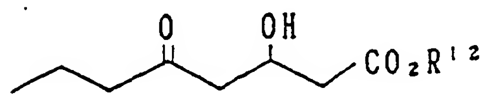


Table 1 (continued)

R^1	R^2	R^3	R^4
H	i-Pr	4-F	H
H	i-Pr	4-F	3-Me
H	i-Pr	4-Cℓ	H
H	i-Pr	H	H
H	c-Pr	4-F	H
H	c-Pr	4-F	3-Me
H	c-Pr	4-Cℓ	H
H	c-Pr	H	H
Me	i-Pr	4-F	H
Me	i-Pr	4-F	3-Me
Me	i-Pr	4-Cℓ	H
Me	i-Pr	H	H
Me	c-Pr	4-F	H
Me	c-Pr	4-F	3-Me
Me	c-Pr	4-Cℓ	H
Me	c-Pr	H	H
Et	i-Pr	4-F	H
Et	i-Pr	4-F	3-Me

Table 1 (continued)

R^1	R^2	R^3	R^4
Et	i-Pr	4-Cℓ	H
Et	i-Pr	H	H
Et	c-Pr	4-F	H
Et	c-Pr	4-F	3-Me
Et	c-Pr	4-Cℓ	H
Et	c-Pr	H	H
i-Pr	i-Pr	4-F	H
i-Pr	i-Pr	4-F	3-Me
i-Pr	i-Pr	4-Cℓ	H
i-Pr	i-Pr	H	H
i-Pr	c-Pr	4-F	H
i-Pr	c-Pr	4-F	3-Me
i-Pr	c-Pr	4-Cℓ	H
i-Pr	c-Pr	H	H
n-Bu	i-Pr	4-F	H
n-Bu	i-Pr	4-F	3-Me
n-Bu	i-Pr	4-Cℓ	H

Table 1 (continued)

R^1	R^2	R^3	R^4
n-Bu	i-Pr	H	H
n-Bu	c-Pr	4-F	H
n-Bu	c-Pr	4-F	3-Me
n-Bu	c-Pr	4-Cℓ	H
n-Bu	c-Pr	H	H
c-Hex	i-Pr	4-F	H
c-Hex	i-Pr	4-F	3-Me
c-Hex	i-Pr	4-Cℓ	H
c-Hex	i-Pr	H	H
c-Hex	c-Pr	4-F	H
c-Hex	c-Pr	4-F	3-Me
c-Hex	c-Pr	4-Cℓ	H
c-Hex	c-Pr	H	H
Ph	i-Pr	4-F	H
Ph	i-Pr	4-F	3-Me
Ph	i-Pr	4-Cℓ	H
Ph	i-Pr	H	H
Ph	c-Pr	4-F	H

Table 1 (continued)

R^1	R^2	R^3	R^4
Ph	c-Pr	4-F	3-Me
Ph	c-Pr	4-Cℓ	H
Ph	c-Pr	H	H
$PhCH_2$	i-Pr	4-F	H
$PhCH_2$	i-Pr	4-F	3-Me
$PhCH_2$	i-Pr	4-Cℓ	H
$PhCH_2$	i-Pr	H	H
$PhCH_2$	c-Pr	4-F	H
$PhCH_2$	c-Pr	4-F	3-Me
$PhCH_2$	c-Pr	4-Cℓ	H
$PhCH_2$	c-Pr	H	H
3-pyridyl	i-Pr	4-F	H
3-pyridyl	i-Pr	4-F	3-Me
3-pyridyl	i-Pr	4-Cℓ	H
3-pyridyl	i-Pr	H	H
3-pyridyl	c-Pr	4-F	H
3-pyridyl	c-Pr	4-F	3-Me

Table 1 (continued)

R^1	R^2	R^3	R^4
3-pyridyl	c-Pr	4-Cℓ	H
3-pyridyl	c-Pr	H	H
4-Cℓ-Ph	i-Pr	4-F	H
4-Cℓ-Ph	i-Pr	4-F	3-Me
4-Cℓ-Ph	i-Pr	4-Cℓ	H
4-Cℓ-Ph	i-Pr	H	H
4-Cℓ-Ph	c-Pr	4-F	H
4-Cℓ-Ph	c-Pr	4-F	3-Me
4-Cℓ-Ph	c-Pr	4-Cℓ	H
4-Cℓ-Ph	c-Pr	H	H
4-MeO-Ph	i-Pr	4-F	H
4-MeO-Ph	i-Pr	4-F	3-Me
4-MeO-Ph	i-Pr	4-Cℓ	H
4-MeO-Ph	i-Pr	H	H
4-MeO-Ph	c-Pr	4-F	H
4-MeO-Ph	c-Pr	4-F	3-Me
4-MeO-Ph	c-Pr	4-Cℓ	H

Table 1 (continued)

R^1	R^2	R^3	R^4
4-MeO-Ph	c-Pr	H	H
4-Me-Ph	i-Pr	4-F	H
4-Me-Ph	i-Pr	4-F	3-Me
4-Me-Ph	i-Pr	4-Cℓ	H
4-Me-Ph	i-Pr	H	H
4-Me-Ph	c-Pr	4-F	H
4-Me-Ph	c-Pr	4-F	3-Me
4-Me-Ph	c-Pr	4-Cℓ	H
4-Me-Ph	c-Pr	H	H
n-octyl	i-Pr	4-F	H
n-octyl	i-Pr	4-F	3-Me
n-octyl	i-Pr	4-Cℓ	H
n-octyl	i-Pr	H	H
n-octyl	c-Pr	4-F	H
n-octyl	c-Pr	4-F	3-Me
n-octyl	c-Pr	4-Cℓ	H
n-octyl	c-Pr	H	H
Vinyl	i-Pr	4-F	H

Table 1 (continued)

R^1	R^2	R^3	R^4
Vinyl	i-Pr	4-F	3-Me
Vinyl	i-Pr	4-Cℓ	H
Vinyl	i-Pr	H	H
Vinyl	c-Pr	4-F	H
Vinyl	c-Pr	4-F	3-Me
Vinyl	c-Pr	4-Cℓ	H
Vinyl	c-Pr	H	H
c-Pr	i-Pr	4-F	H
c-Pr	i-Pr	4-F	3-Me
c-Pr	i-Pr	4-Cℓ	H
c-Pr	i-Pr	H	H
c-Pr	c-Pr	4-F	H
c-Pr	c-Pr	4-F	3-Me
c-Pr	c-Pr	4-Cℓ	H
c-Pr	c-Pr	H	H
MeO	i-Pr	4-F	H
MeO	i-Pr	4-F	3-Me

Table 1 (continued)

R^1	R^2	R^3	R^4
MeO	i-Pr	4-Cℓ	H
MeO	i-Pr	H	H
MeO	c-Pr	4-F	H
MeO	c-Pr	4-F	3-Me
MeO	c-Pr	4-Cℓ	H
MeO	c-Pr	H	H
MeS	i-Pr	4-F	H
MeS	i-Pr	4-F	3-Me
MeS	i-Pr	4-Cℓ	H
MeS	i-Pr	H	H
MeS	c-Pr	4-F	H
MeS	c-Pr	4-F	3-Me
MeS	c-Pr	4-Cℓ	H
MeS	c-Pr	H	H
Cℓ	i-Pr	4-F	H
Cℓ	i-Pr	4-F	3-Me
Cℓ	i-Pr	4-Cℓ	H

Table 1 (continued)

R^1	R^2	R^3	R^4
Cℓ	i-Pr	H	H
Cℓ	c-Pr	4-F	H
Cℓ	c-Pr	4-F	3-Me
Cℓ	c-Pr	4-Cℓ	H
Cℓ	c-Pr	H	H
Br	i-Pr	4-F	H
Br	i-Pr	4-F	3-Me
Br	i-Pr	4-Cℓ	H
Br	i-Pr	H	H
Br	c-Pr	4-F	H
Br	c-Pr	4-F	3-Me
Br	c-Pr	4-Cℓ	H
Br	c-Pr	H	H
3-CF_3-Ph	i-Pr	4-F	H
3-CF_3-Ph	i-Pr	4-F	3-Me
3-CF_3-Ph	i-Pr	4-Cℓ	H
3-CF_3-Ph	i-Pr	H	H

Table 1 (continued)

R^1	R^2	R^3	R^4
$3\text{-}CF_3\text{-}Ph$	c-Pr	4-F	H
$3\text{-}CF_3\text{-}Ph$	c-Pr	4-F	3-Me
$3\text{-}CF_3\text{-}Ph$	c-Pr	4-Cℓ	H
$3\text{-}CF_3\text{-}Ph$	c-Pr	H	H
4-c-Pr-Ph	i-Pr	4-F	H
4-c-Pr-Ph	i-Pr	4-F	3-Me
4-c-Pr-Ph	i-Pr	4-Cℓ	H
4-c-Pr-Ph	i-Pr	H	H
4-c-Pr-Ph	c-Pr	4-F	H
4-c-Pr-Ph	c-Pr	4-F	3-Me
4-c-Pr-Ph	c-Pr	4-Cℓ	H
4-c-Pr-Ph	c-Pr	H	H
2- furyl	i-Pr	4-F	H
2- furyl	i-Pr	4-F	3-Me
2- furyl	i-Pr	4-Cℓ	H
2- furyl	i-Pr	H	H
2- furyl	c-Pr	4-F	H

Table 1 (continued)

R[1]	R[2]	R[3]	R[4]
2-furyl	c-Pr	4-F	3-Me
2-furyl	c-Pr	4-Cℓ	H
2-furyl	c-Pr	H	H
2-thienyl	i-Pr	4-F	H
2-thienyl	i-Pr	4-F	3-Me
2-thienyl	i-Pr	4-Cℓ	H
2-thienyl	i-Pr	H	H
2-thienyl	c-Pr	4-F	H
2-thienyl	c-Pr	4-F	3-Me
2-thienyl	c-Pr	4-Cℓ	H
2-thienyl	c-Pr	H	H
2-pyrimidyl	i-Pr	4-F	H
2-pyrimidyl	i-Pr	4-F	3-Me
2-pyrinidyl	i-Pr	4-Cℓ	H
2-pyrimidyl	i-Pr	H	H
2-pyrimidyl	c-Pr	4-F	H
2-pyrimidyl	c-Pr	4-F	3-Me

Table 1 (continued)

R^1	R^2	R^3	R^4
2-pyrimidyl	c-Pr	4-Cℓ	H
2-pyrimidyl	c-Pr	H	H
PhO	i-Pr	4-F	H
PhO	i-Pr	4-F	3-Me
PhO	i-Pr	4-Cℓ	H
PhO	i-Pr	H	H
PhO	c-Pr	4-F	H
PhO	c-Pr	4-F	3-Me
PhO	c-Pr	4-Cℓ	H
PhO	c-Pr	H	H
$N(Me)_2$	i-Pr	4-F	H
$N(Me)_2$	i-Pr	4-F	3-Me
$N(Me)_2$	i-Pr	4-Cℓ	H
$N(Me)_2$	i-Pr	H	H
$N(Me)_2$	c-Pr	4-F	H
$N(Me)_2$	c-Pr	4-F	3-Me
$N(Me)_2$	c-Pr	4-Cℓ	H

Table 1 (continued)

R^1	R^2	R^3	R^4
$N(Me)_2$	c-Pr	H	H
2-Phenethyl	i-Pr	4-F	H
2-Phenethyl	i-Pr	4-F	3-Me
2-Phenethyl	i-Pr	4-Cℓ	H
2-Phenethyl	i-Pr	H	H
2-Phenethyl	c-Pr	4-F	H
2-Phenethyl	c-Pr	4-F	3-Me
2-Phenethyl	c-Pr	4-Cℓ	H
2-Phenethyl	c-Pr	H	H
α-naphthyl	i-Pr	4-F	H
α-naphthyl	i-Pr	4-F	3-Me
α-naphthyl	i-Pr	4-Cℓ	H
α-naphthyl	i-Pr	H	H
α-naphthyl	c-Pr	4-F	H
α-naphthyl	c-Pr	4-F	3-Me
α-naphthyl	c-Pr	4-Cℓ	H
α-naphthyl	c-Pr	H	H

Table 1 (continued)

R^1	R^2	R^3	R^4
Ph	i-Pr	4-c-Pr	H
Ph	c-Pr	4-c-Pr	H
Ph	i-Pr	4-MeO	H
Ph	c-Pr	4-MeO	H
Ph	i-Pr	$4\text{-}N(Me)_2$	H
Ph	c-Pr	$4\text{-}N(Me)_2$	H
Ph	i-Pr	$3\text{-}CF_3$	H
Ph	c-Pr	$3\text{-}CF_3$	H
Ph	i-Pr	4-Ph	H
Ph	c-Pr	4-Ph	H
Ph	i-Pr	4-OH	H
Ph	c-Pr	4-OH	H
Ph	i-Pr	$4\text{-}OCH_2Ph$	H
Ph	c-Pr	$4\text{-}OCH_2Ph$	H
Ph	i-Pr	$4\text{-}OSiMe_3$	H
Ph	c-Pr	$4\text{-}OSiMe_3$	H
Ph	i-Pr	$4\text{-}CH_2OH$	H

Table 1 (continued)

R^1	R^2	R^3	R^4
Ph	c-Pr	4-CH_2OH	H
Ph	i-Pr	4-OCH_2CH_2OMe	H
Ph	c-Pr	4-OCH_2CH_2OMe	H
Ph	i-Pr	3,4-OCH_2O-	
Ph	c-Pr	3,4-OCH_2O-	
Ph	i-Pr	3,4-CH=CH-CH=CH	
Ph	c-Pr	3,4-CH=CH-CH=CH	
Ph	Me	4-F	H
Ph	Me	4-F	3-Me
Ph	Me	4-Cℓ	H
Ph	Me	H	H
Ph	Et	4-F	H
Ph	Et	4-F	3-Me
Ph	Et	4-Cℓ	H
Ph	Et	H	H
Ph	n-Pr	4-F	H
Ph	n-Pr	4-F	3-Me

Table 1 (continued)

R^1	R^2	R^3	R^4
Ph	n-Pr	4-Cℓ	H
Ph	n-Pr	H	H
Ph	n-Hex	4-F	H
Ph	n-Hex	4-F	3-Me
Ph	n-Hex	4-Cℓ	H
Ph	n-Hex	H	H
Ph	$-C(CH_2)=CH_2$	4-F	H
Ph	$-C(CH_2)=CH_2$	4-F	3-Me
Ph	$-C(CH_2)=CH_2$	4-Cℓ	H
Ph	$-C(CH_2)=CH_2$	H	H
Ph	c-Hex	4-F	H
Ph	c-Hex	4-F	3-Me
Ph	c-Hex	4-Cℓ	H
Ph	c-Hex	H	H
Ph	3-c-Pentenyl	4-F	H
Ph	3-c-Pentenyl	4-F	3-Me
Ph	3-c-Pentenyl	4-Cℓ	H

Table 1 (continued)

R^1	R^2	R^3	R^4
Ph	3-c-Pentenyl	H	H
Ph	Ph	4-F	H
Ph	Ph	4-F	3-Me
Ph	Ph	4-Cℓ	H
Ph	Ph	H	H
Ph	CH_2Ph	4-F	H
Ph	CH_2Ph	4-F	3-Me
Ph	CH_2Ph	4-Cℓ	H
Ph	CH_2Ph	H	H

Further, pharmaceutically acceptable salts such as potassium salts, 1/2 calcium salts, esters such as methyl ester, n-propyl ester, i-propyl ester, c-propyl ester, n-butyl ester, i-butyl ester, sec-butyl ester, t-butyl ester, n-pentyl ester, i-pentyl ester and n-hexyl ester, or ammonium salts or trimethylamine salts of these compounds can be prepared in the same manner.

The compounds of the present invention exhibit high inhibitory activities against the cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme, as shown by the test results given hereinafter, and thus are capable of suppressing or ruducing the amount of cholesterol in blood as lipoprotein. Thus, the compounds of the present invention are useful as curing agents against hyperlipidemia, hyperlipoproteinemia and atheroscleosis.

They may be formulated into various suitable formulations depending upon the manner of the administration. The compounds of the present invention may be administered in the form of free acids or in the form of physiologically hydrolyzable and acceptable esters or lactones, or pharmaceutically acceptable salts.

The pharmaceutical composition of the present invention is preferably administered orally in the form of the compound of the present invention by itself or in the form of powders, granules, tablets or capsules formulated by mixing the compound of the present invention with a suitable pharmaceutically acceptable carrier including a binder such as hydroxypropyl cellulose, syrup, gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone or CMC-Ca, an excipient such as lactose, sugar, corn starch, calcium phosphate, sorbitol, glycine or crystal cellulose powder, a lubricant such as magnesium stearate, talc, polyethylene glycol or silica, and a disintegrator such as potato starch.

However, the pharmaceutical composition of the present invention is not limited to such oral administration and it is applicable for parenteral administration. F r example, it may be administered in the form of e.g. a suppository formulated by using oily bas material such as cacao butter, polyethylene glycol, lanolin or fatty acid triglyceride, a transdermal therapeutic bas formulated by using liquid paraffin, white vaseline, a higher alcohol, Macrogol ointment, hydrophilic ointment or hydro-gel base material, an injection formulation formulated by using one or more materials selected from th group consisting of polyethylene glycol, hydro-gel base material, distilled water, distilled water for injection and an excipient such as lactose or corn starch, or a formulation for administration through mucous memberanes such as an ocular mucous membrane, a nasal mucous membrane and an oral mucous membrane.

Further, the compounds of the present invention may be combined with basic ion-exchange resins which are capable of binding bile acids and yet not being absorbed by the gastroint stinal tract.

The daily dose of the compound is from 0.05 to 500 mg, preferably from 0.5 to 50 mg, for an adult. It is administered from once to three times per day. The dose may of course be varied depending upon the age, the weight or the condition of illness of th patient.

The compounds of the formulas II to X are novel, and they are important intermediates for the preparation of the compounds of the formula I. Accordingly, the present invention relates also to the compounds of the formulas II to X and the processes for their production.

Now, the present invention will be described in further detail with reference to Test Examples for the pharmacological activities of the compounds of the present invention, their Preparation Examples and formulation Examples. However, it should be understood that the present invention is by no menas restricted by such specific Examples.

PHARMACOLOGICAL TEST EXAMPLES

Test A: Inhibition of cholesterol biosynthesis from' acetate in vitro

Enzyme solution was prepared from liver of male Wistar rat billialy connulated and discharged bile for over 24 hours. Liver was cut out at mid-dark and microsome and supernatant fraction which was precipitable with 40-80% of solution of ammonium sulfate (sup fraction) were prepared from liver homogenate according to the modified method of Knauss et. al.; Kuroda, M., et. al., Biochim. Biophys. Acta, 489, 119 (1977). For assay of cholesterol biosynthesis, microsome (0.1 mg protein) and sup fraction (1.0 mg protein) were incubated for 2 hours at 37°C in 200 µl of the reaction mixture containing ATP; 1 mM, Glutathione; 6 mM, Glucose-1-phosphate; 10 mM, NAD; 0.25 mM, NADP; 0.25 mM, CoA; 0.04 mM and 0.2 mM [2-^{14}C]sodium acetate (0.2 µCi) with 4 µl of test compound solution dissolved in water or dimethyl sulfoxide. To stop reaction and saponify, 1 ml of 15% EtOH-KOH was added to the reactions and heated at 75°C for 1 hour. Nonsaponifiable lipids were extracted with petroleum ether and incorporated ^{14}C radioactivity was counted. Inhibitory activity of compounds was indicated with IC50.

Test B: Inhibition of cholesterol biosynthesis in culture cells

Hep G2 cells at over 5th passage were seeded to 12 well plates and incubated with Dulbecco's modified Eagle (DME) medium containing 10% of fetal bovine serum (FBS) at 37°C, 5% CO_2 until cells were confluent for about 7 days. Cells were exposed to the DME medium contaiing 5% of lipoprotein deficient serum (LpDS) prepared by ultracentrifugation method for over 24 hours. Medium was changed to 0.5 ml of fresh 5% LpDS containing DME before assay and 10 µl of test compound solution dissolved in water or DMSO were added. 0.2 µci of [2-^{14}C]sodium acetate (20 µl) was added at 0 hr(B-1) or 4 hrs(B-2) after addition of compounds. After 4 hrs further incubation with [2-^{14}C]sodium acetate, medium was removed and cells were washed with phosphate buffered saline (PBS) chilled at 4°C. Cells were scraped with rubber policeman and collected to tubes with PBS and digested with 0.2 ml of 0.5 N KOH at 37°C. Aliquot of digestion was used for protein analysis and remaining was saponified with 1 ml of 15% EtOH-KOH at 75°C for 1 hour. Nonsaponifiable lipids were extracted with petroleum ether and ^{14}C radioactivity was counted. Counts were revised by cell protein and indicated with DPM/mg protein. Inhibitory activity of compounds was indicated with IC50.

Test C: Inhibition of cholesterol biosynthesis in vivo

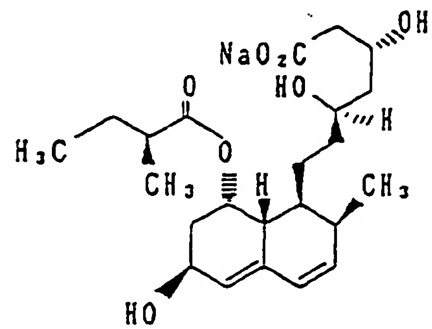
Male Sprague-Dawley rats weighing about 150 g were fed normal Purina chow diet and water ad libitum, and exposed to 12 hours light/12 hours dark lighting pattern (2:00 PM - 2:00 AM dark) prior to use for in vivo inhibition test of cholesterol biosynthesis. Animals were separated groups consisting of five rats as to be average mean body weight in each groups. Test compounds at dosage of 0.02-2.0 mg/kg body weight (0.4 ml/100 g body weight), were dissolved in water or suspended in 0.5% methyl cellulose and orally administered at 2-3 hours before mid-dark (8:00 PM), while chol sterol biosynthesis reaches to maximum in rats. As control, rats were orally administered only water or vehicle. At 90 minutes after sample

administration, rats were injected intraperitoneally with 10 μCi of [2-^{14}C]sodium acetate at volume of 0.2 ml per one. 2 Hours later, blood samples were obtained and serum were separated immediately. Total lipids were extracted according to the method of Folch et al. and saponified with EtOH-KOH. Nonsaponifiable lipids were extracted with petroleum ether and radio activity incorporated into nonsaponifiable lipids was counted.

Inhibitory activity was indicated as percent decrease of counts in testing groups (DPM/2 ml serum/2 hours) from that in control group.

With respect to the compounds of the present invention, the inhibitory activities against the cholesterol biosynthesis in which HMG-CoA reductase serves as a rate limiting enzyme, were measured by the above Test A and B. The results are shown in Tables 2 and 3.

The chemical structure of Reference Compound is shown as follows.



IC_{50} of CS-514 in Test A was 9.0×10^{-9} M/ℓ.

The relative activities of the compounds of the present invention based on the activities of CS-514 by Test A being evaluated to be 1, are shown in Table 2.

Table 2

Relative activities by Test A	
Compound of the present invention	Relative activities
I-1-1	1.6
I-5-1	1.3
I-5-2	0.6

In Table 3, the inhibition activites of the test compounds at a concentration of 100×10^{-9} M/ℓ, are shown.

Table 3

Inhibition activities by Test B-1	
Compound of the present invention	Inhibition activities
(Reference compound)	
CS-514	18.4
(Compound of the present invention)	
I-1-1	50.1
I-1-2	57.3
I-5-2	43.2
II-1	52.6

Results of the measurement of the inhibitory activities by Test C

The percent decreases of counts after the oral administration of 0.2 mg/kg of compound I-5-2 was 34.3%, relative to the measured value of the control group. The percent decrease of counts after the oral administration of 0.2 mg/kg of CS-514 was 34% under the same condition.

As is evident from the foregoing, the compounds of the present ivention exhibited activities equivalent or superior to the reference compound CS-514 in Tests A, B-1 and C.

Test D: Acute toxicity

A 0.5% CMC suspension of a test compound was orally administered to ICR male mice (group of three mice). The acute toxicity was determined based on the mortality after seven darys. With compound I-5-2 of the present ivnention, only one animal of the three animals died.

EXAMPLE 1

Ethyl (E)-7-[4′-(4″-fluorophenyl)-3′-methyl-6′-(1″-methylethyl)isoxazolo[5,4-b]pyridin-5′-yl]-3,5-dihydroxyhept-6-enoate (compound I-1-1)

This compound was prepared by the synthesis comprising the following reaction steps Example 1-a_0 to Example 1-f.

EXAMPLE a_0-1

Ethyl 4-(4′-fluorophenyl)-3-methyl-6-(1′-methylethyl)-4,7-dihydroisoxazolo[5,4-b]pyridin-5-ylcarboxylate (Compound X-1)

This compound was prepared in accordance with the method disclosed in Japanese Unexamined Patent Publication No. 152386/1984.

4.90 g (5×10^{-2} mol of 5-amino-3-m thylisoxazole (Compound XI-1) and 13.20 g (5×10^{-2} mol) of ethyl 2-(4′-fluorobenzylidene)-4-methyl-3-oxopentanoate (Compound XII-1) were dissolved in tert-butyl alcohol, and the solution was heated at 80°C for about day and night. After confirming the complete

disappearance of the starting materials by thin layer chromatography, the solvent was distilled off under reduced pressure from the reaction solution by an evaporator. The residual oil was subjected to silica gel column chromatography (eluent: benzene/ethyl acetate) to obtain 5.57 g (yield: 32.4%) of the desired compound as slightly yellow oily substance.

EXAMPLE a_0-2

Ethyl 4-(4′-fluorophenyl)-3-methyl-6-(1′-methylethyl)isoxazolo[5,4-b]pyridin-5-ylcarboxylate (Compound VII-1)

9.00 g (2.62 × 10^{-2} mol) of Compound X-1 was dissolved in 100 ml of acetone dehydrated by Molecular Sieves, and 6.21 g of potassium permanganate was added thereto. The mixture was stirred at room temperature.

Four hours later, the disappearance of the starting material was cofirmed by thin layer chromatography, and then, the reaction mixture was subjected to filtration to remove insolubles. The solvent was distilled off under reduced pressure from the filtrate by an evaporator. The residual solid was dissolved benzene, and the solution was subjected to activated carbon treatment. Then, the solvent was distilled off to obtain 6.55 g (73.1 %) of the desired compound as brown powder.

Melting point: 95-102°C

EXAMPLE 1-a

4-(4′-fluorophenyl)-5-hydroxymethyl-3-methyl-6-(1′-methylethyl)isoxazolo[5,4-b]pyridine (Compound VI-1)

6.55 g (1.92 × 10^{-2} mol) of Compound VII-1 was dissolved in 100 ml of toluene dehydrated by Molecular Sieves, and the solution was cooled to -10°C under a nitrogen atmosphere and stirred.

To this solution, 57.6 ml of a 16 weight % dibutylaluminum hydride-toluene solution was gradually dropwise added, and the mixture was stirred at -10°C for 2.5 hours.

After confirming the disappearance of the starting material by thin layer chromatography, 100 ml of diethyl ether was added to the reaction solution, and cold and diluted hydrochloric acid was carefully dropwise added thereto to terminate the reaction. The ether layer was separated, washed twice with a saturated sodium chloride aqueous solution, then dried over anhydrous magnesium sulfate and subjected to filtration. The solvent was distilled off by an evaporator and a vacuum pump, and the residual solid was subjected to silica gel column chromatography (eluent: benzene/ethyl acetate) to obtain 2.27 g (yield: 39.4%) of the desired compound as slighytly yellow powder.

Melting point: 90-110°C

EXAMPLE 1-b

4-(4′-fluorophenyl)-3-methyl-6-(1′-methylethyl)-isoxazolo[5,4-b]pyridin-5-ylcarboxyaldehyde (Compound V-1)

2.27 g (7.57 × 10^{-3} mol) of Compound VI-1 was dissolved in 20 ml of dichloromethane dehydrated by Molecular Sieves, and 0.15 g of anhydrous sodium acetate was added thereto to prepare a suspension. 1.89 g (8.77 × 10^{-3} mol) of powder of pyridinium chlorochromate was gradually addded to the suspension under cooling with ice and stirring, and the mixture was stirred at room temperature for about 11 hours. After confirming the disappearance of the starting materials by thin layer chromatography, 100 ml of diethyl ether was added thereto, and the mixture was stirred.

The reaction mixture was subjected to suction filtration through a silica gel layer. The residual tar was sufficiently washed with diethyl ether until the tar became powder. The washing solution was subjected to filtration through the silica gel layer and put together with the above-mentioned filtrate. The solvent was evaporated by an vaporator. The residue was dissolv d in benzene, and the benzene solution was

subjected to activated carbon treatment. The crude crystal obtained by distillation of the solvent, was subjected to silica gel column chromatography (eluent: benzene/ethyl acetate) to obtain 1.75 g (yield: 77.6%) of the desired compound as slightly yellow powder.

Melting point: 76-81 °C

EXAMPLE 1-c

5-(3′-ethoxy-1′-hydroxy-2′-propen-1′-yl)-4-(4′-fluorophenyl)-3-methyl-6-(1′-methylethyl)isoxazolo[5,4-b]-pyridine (Compound IV-1)

4.23 g (11.7 mmol) of cis-1-ethoxy-2-(tri-n-butylstannyl)ethylene was dissolved in 120 ml of dry tetrahydrofuran, and the solution was cooled to -78 °C under a nitrogen atmosphere. 7.97 ml (12.9 mmol) of a 15 weight % n-butyl lithium-n-hexane solution was dropwise added to this solution. The mixture was stirred for 20 minutes, and then, a solution of 1.75 g (5.87 mmol) of Compound V-1 dissolved in 120 ml of dry tetrahydrofuran was dropwise added thereto. The reaction mixture was stirred at -78 °C for 1.5 hours, and then, 5 ml of a saturated ammonium chloride solution was added thereto to terminate the reaction. The organic layer was extracted with diethyl ether. The ether extract was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magensium sulfate. The solvent was distilled off under reduced pressure, and the residue was subjected to liquid separation between n-hexane and acetonitrile. The acetonitrile layer was subjected to distillation under reduced pressure to obtain the desired compound as slightly yellow powder.

Melting point: 35-40 °C

EXAMPLE 1-d

(E)-3-[4′-(4″-fluorophenyl)-3′-methyl-6′-(1″-methylethyl)isoxazolo[5,4-b]pyridin-5′-yl]-2-propenal (Compound III-1)

1.96 g of Compound IV-1 was dissolved in 40 ml of tetrahydrofuran, and 10 ml of water and 50 mg of p-toluenesulfonic acid were added thereto. The mixture was stirred at room temperature for 3 hours. Diethyl ether was added to the reaction solution, and the extraction was conducted a few times. The extract was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (eluent: 50% ethyl acetate/benzene) to obtain the desired compound as slightly yellow powder.

Melting point: 127-129 °C

EXAMPLE 1-e

Ethyl (E)-7-[4′-(4″-fluorophenyl)-3′-methyl-6′-(1″-methylethyl)isoxazolo[5,4-b]pyridin-5′-yl]-5-hydroxy-3-oxohepto-6-enoate (Compound II-1)

0.25 g of 55 wt % sodium hydride was washed with dry hexane, dried under a nitrogen stream and then suspended in 65 ml of dry tetrahydrofuran. The suspension was stirred to -15 °C under a nitrogen atmosphere, and 0.71 g (5.46 × 10^{-3} mol of ethyl acetoacetate was gradually dropwise added thereto. The mixture was stirred at -15 °C for 20 minutes. Then, 3.33 ml (5.39 × 10^{-3} mol) of a 1.62 M/ℓ n-butyl lithium-n-hexane solution was dropwis added thereto, and th mixture was stirred for 20 minutes. Further, a solution of 1.04 g (3.21 × 10^{-3} mol of Compound III-1 dissolved in 25 ml of dry tetrahydrofuran was dropwise added thereto, and the mixture was stirred for 5 hours. A cold saturated ammonium chloride aqueous solution was added to the r action mixture, and the mixture was extracted with diethyl ether. The ether layer was washed with a saturated sodium chlorid aqueous solution, dried over anhydrous magnesium sulfate and then subjected to filtration. The solvent was evaporated by an evaporator. The residue was

subjected to silica gel column chromatography (eluent: benzene/ethyl acetate) to obtain 0.57 g (yield: 39.1%) of the desired compound as slightly brown powder.

Melting point: 104-110 °C

EXAMPLE 1-f

Ethyl (E)-7-[4′-(4″-fluorophenyl)-3′-methyl-6′-(1″-methylethyl)isoxazolo[5,4-b]pyridin-5′-yl]-3,5-dihydroxyhept-6-enoate (Compound I-1-1)

20 ml (about 3 x 10^{-3} mol) of a diethyl ether solution of about 0.15 mol/ℓ of zinc borohydride was cooled to -70 °C under a nitrogen atmosphere. A solution of 295 mg (6.5 x 10^{-3} mol) of Compound II-1 dissolved in 40 ml of dry diethyl ether was gradually added thereto. Further, the reaction solution was stirred at -70 °C for 2 hours. After confirming the disappearance of the starting material II-1 by thin layer chromatography, 3 ml of methanol and then 10 ml of water was added thereto at -70 °C to terminate the reaction. Further, 120 ml of water and 120 ml of diethyl ether was added thereto and a diluted acetic acid aqueous solution was added thereto to adjust pH to 4, and the product was extracted with diethyl ether.

The diethyl ether layer was washed with water and with a saturated sodium chloride aqueous solution. The diethyl ether layer was dried over anhydrous magnesium sulfate, and then, the solvent was evaporated by an evaporator. The residual oil was subjected to silica gel column chromatography (eluent: benzene/ethyl acetate) to obtain 140 mg (yield: 47.3%) of the desired compound as slightly yellow powder.

Melting point: 98-104 °C

MS (m/e, FAB): 457(M+H)

NMR (in $CDCl_3$) δppm: 1.29(t,3H,J=7Hz), 1.33(d,6H,J=7Hz), 1.3-1.5(m,2H), 1.97(s,3H) 2.3-2.5(m,2H), 3.2-3.8(m,2H), 3.47(Heptalet,1H,J=7Hz), 4.19(q,2H,J=7Hz), 4.0-4.5(m,2H), 5.34(dd,1H,J=6Hz,17Hz), 6.52-(d,1H,J=17Hz), 7.1-7.4(m,4H)

EXAMPLE 2

Sodium (E)-7-4′-(4″-fluorophenyl)-3′-methyl-6′-(1″-methylethyl)isoxazolo[5,4-b]pyridin-5′-yl]-3,5-dihydroxyhept-6-enoate (Compound I-5-1: sodium salt of Compound I-1-1)

89.6 mg (1.96 x 10^{-4} mol) of Compound I-1-1 was dissolved in 3 ml of ethanol, and 0.37 ml of a 0.5 N sodium hydroxide aqueous solution was dropwise added thereto. The mixture was stirred at room temperature for 4 hours. Then, ethanol was distilled off under reduced pressure at 45 °C, 5 ml of distilled water was added thereto, and the residual starting material was extracted with diethyl ether. The aqueous layer was freeze-dried to obtain 88.2 mg (yield: 100%) of hygroscopic slightly yellow powder.

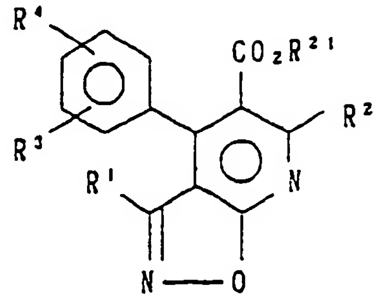
Melting point: 125-130 °C

MS (m/e, FAB): 473(M+Na), 451(M+H), 329

NMR (in d_6-DMSO) δppm: 1.09-1.5(m,2H), 1.26(d,6H,J=7Hz), 1.89(s,3H), 1.6-2.1(m,2H), 2.9-3.8(m,3H), 3.52-(Heptalet,1H,J=7Hz), 3.9-4.3(m,1H), 5.40(dd,1H,J=6Hz,17Hz), 6.38(d,1H,J=17Hz), 7.1-7.5(m,4H)

In the same manner as in Example 1-a_0 (a_0-1 ~ a_0-2), Compound VII-2 was prepared.

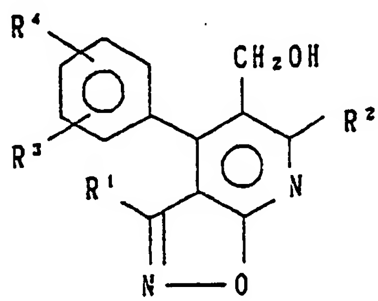
Table 4



Compound	R^1	R^2	R^3	R^4	R^{21}	Melting point (°C)
VII − 2	Ph	i-Pr	4-F	H	Et	104-106

In the same manner as in Example 1-a, Compound VI-2 was prepared.

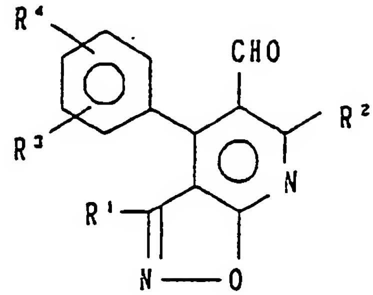
Table 5



Compound	R^1	R^2	R^3	R^4	Melting point (°C)
VI − 2	Ph	i-Pr	4-F	H	140-150

In the same manner as in Example 1-b, Compound V-2 was prepared.

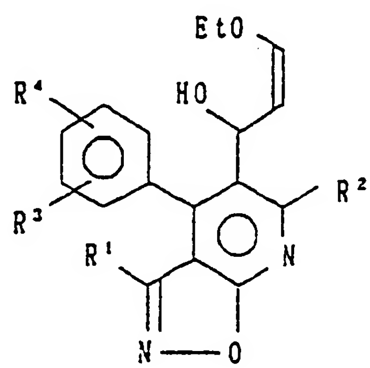
Table 6



Compound	R¹	R²	R³	R⁴	Melting point (°C)
V - 2	Ph	i-Pr	4-F	H	141-149

In the same manner as in Example 1-c, Compound IV-2 was prepared.

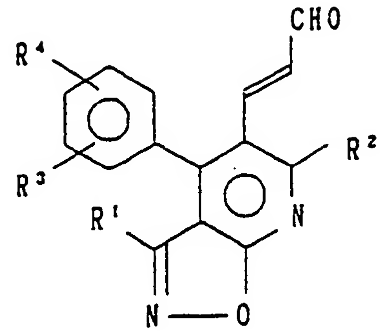
Table 7



Compound	R¹	R²	R³	R⁴	Melting point (°C)
IV - 2	Ph	i-Pr	4-F	H	42-47

In the same manner as fin Example 1-d, Compound III-2 was prepared.

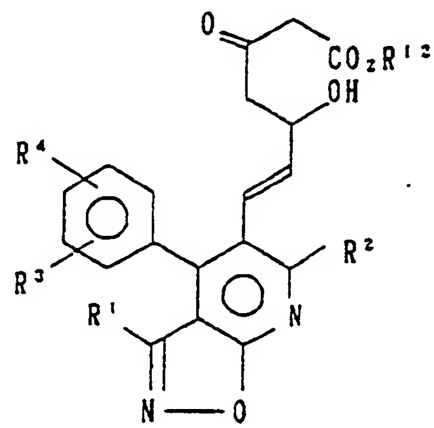
Table 8



Compound	R^1	R^2	R^3	R^4	Melting point (°C)
III − 2	Ph	i-Pr	4-F	H	185-186.5

In the same manner as in Example 1-e, Compound II-2 was prepared.

Table 9

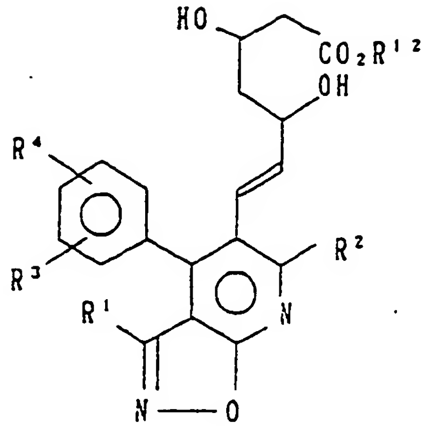


Compound	R^1	R^2	R^3	R^4	R^{12}	Melting point (°C)
II − 2	Ph	i-Pr	4-F	H	Et	Oil

NMR (in $CDCl_3$) δppm: 1.30(t,3H,J=7Hz), 1.35(d,6H,J=7Hz), 2.4-2.7(m,2H), 3,2-3.8(m,2H), 3.45(s,2H), 4.20-(q,2H,J=7Hz), 4.4-4.9(m,1H), 5.43(dd,1H,J=17Hz), 6.70(d,1H,J=17Hz), 6.7-7.5(m,9H)

In the same manner as in Example 1-f, Compound I-1-2 was prepared.

Table 10



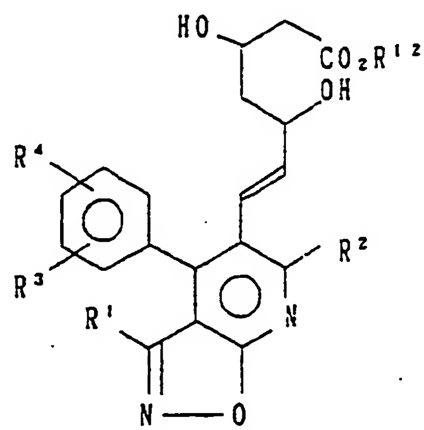
Compound	R^1	R^2	R^3	R^4	R^{12}	Melting point (°C)
I-1-2	Ph	i-Pr	4-F	H	Et	100-103

MS (m/e): 518, 516, 482, 357

NMR (in $CDCl_3$) δppm: 1.28(t,3H,J=7Hz), 1.37(d,6H,J=7Hz), 1.2-1.5(m,2H), 2.3-2.5(m,2H), 2.6-3.1(m,2H), 3.52(Heptalet,1H,J=7Hz), 4.18(q,2H,J=7Hz), 3.9-4.5(m,2H), 5.28(dd,1H,J=6Hz,17Hz), 6.57(d,1H,J=17Hz), 6.7-7.5(m,9H)

In the same manner as in Example 2, Compound I-5-2 was prepared.

Table 11



Compound	R^1	R^2	R^3	R^4	R^{12}	Melting point (°C)
I-5-2	Ph	i-Pr	4-F	H	Na	123-125

MS (m/e, FAB): 535(M+N2), 513(M+H), 414

NMR (in d_6-DMSO) δppm: 0.8-1.3(m,2H), 1.30(d,6H,J=7Hz), 1.7-2.1(m,3H), 3.1-3.8(m,3H), 3.9-4.3(m,1H), 5.36(dd,1H,J=6Hz, 17Hz), 6.42(d,1H,J=17Hz), 6.6-7.5(m,9H)

FORMULATION EXAMPLE 1	
Tablets	
Compound I-5-1	1.0 g
Lactose	5.0 g
Crystal cellulose powder	8.0 g
Corn starch	3.0 g
Hydroxypropyl cellulose	1.0 g
CMC-Ca	1.5 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were mixed by a usual method and then tabletted to produce 100 sugar coating tablets each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 2	
Capsules	
Compound I-5-1	1.0 g
Lactose	3.5 g
Crystal cellulose powder	10.0 g
Magnesium stearate	0.5 g
Total	15.0 g

The above components were mxied by a usual method and then packed in No. 4 gelatin capsules to obtain 100 capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 3	
Soft capsules	
Compound I-5-1	1.00 g
PEG (polyethylene glycol) 400	3.89 g
Saturated fatty acid triglyceride	15.00 g
Peppermint oil	0.01 g
Polysorbate 80	0.10 g
Total	20.00 g

The above components were mixed and packed in No. 3 soft gelatin capsules by a usual method to obtain 100 soft capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 4		
Ointment		
Compound I-5-1	1.0 g	(10.0 g)
Liquid Paraffin	10.0 g	(10.0 g)
Cetanol	20.0 g	(20.0 g)
White vaseline	68.4 g	(59.4 g)
Ethylparaben	0.1 g	(0.1 g)
ℓ-menthol	0.5 g	(0.5 g)
Total	100.0 g	

The above components were mixed by a usual method to obtain a 1% (10%) ointment.

FORMULATION EXAMPLE 5	
Suppository	
Compound I-5-1	1.0 g
Witepsol H15*	46.9 g
Witepsol W35*	52.0 g
Polysorbate 80	0.1 g
Total	100.0 g

*: Trademark for triglyceride compound

The above components were melt-mixed by a usual method and poured into supository containers, followed by cooling for solidification to obtain 100 suppositories of 1 g each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 6	
Injection formulation	
Compound I-5-1	1 mg
Distilled water for injection formulation	5 mℓ

The formulation is prepared by dissolving the compound in the distilled water whenever it is required.

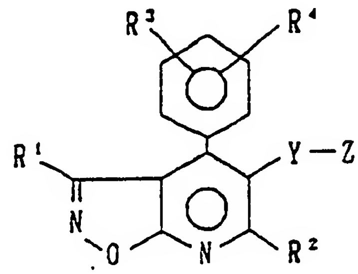
FORMULATION EXAMPLE 7	
Granules	
Compound I-5-1	1.0 g
Lactose	6.0 g
Crystal cellulose powder	6.5 g
Corn starch	5.0 g
Hydroxypropyl cellulose	1.0 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were granulated by a usual method and packaged to obtain 100 packages each

containing 200 mg of th granules so that each package contains 10 mg of the active ingredient.

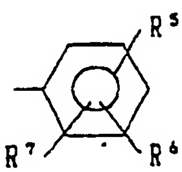
Claims

1. The compound of the formula:

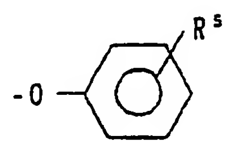


(I)

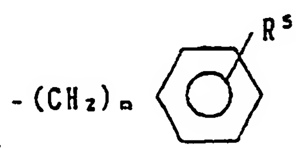
wherein R^1 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, fluoro, chloro, bromo,



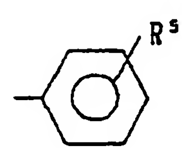
(wherein R^5, R^6 and R^7 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro or bormo), 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, 2- or 5-pyrimidyl,



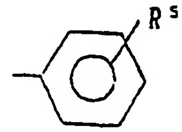
(wherein R^5 is as defined above) or $-NR^8R^9$ (wherein R^8 and R^9 are independently hydrogen, C_{1-4} alkyl or



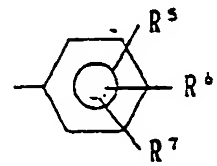
(wherein R^5 is as defined above, and m is 1, 2 or 3) or R^8 and R^9 together form $-(CH_2)_j-$ (wherein j is 3, 4 or 5)); or C_{1-3} alkyl substituted by



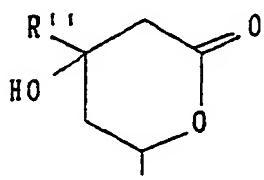
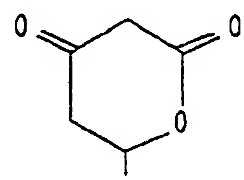
(wherein R^5 is as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-8} alkyl, or α-or β-naphtyl; R^2 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl or

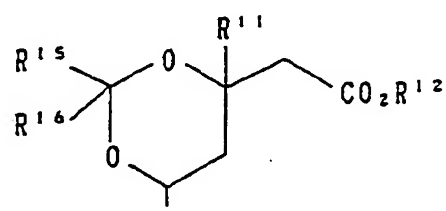


(wherein R^5 is as defined above), or C_{1-3} alkyl substituted by



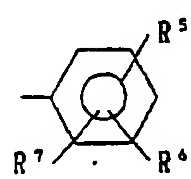
(wherein R^5, R^6 and R^7 are as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-3} alkyl; R^3 and R^4 are independently hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, t-butoxy, $R^{23}R^{24}N$- (R^{23} and R^{24} are independently hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $-O(CH_2)_{\ell}OR^{10}$ (wherein R^{10} is hydrogen, or C_{1-3} alkyl, and ℓ is 1, 2 or 3); or when located at the ortho position to each other, R^3 and R^4 may together form -CH = CH-CH = CH- or methylenedioxy; Y is
$-CH_2$-, $-CH_2CH2$-, -CH = CH-, $-CH_2$-CH = CH-, -CH = CH-CH_2-, $-C(CH_3)$ = CH- or -CH = $C(CH_3)$-; and Z is -Q-CH_2WCH_2-CO_2R^{12},

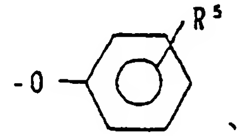


(wherein Q is -C(O)-, $-C(OR^{13})_2$- or -CH(OH)-; W is -C(O)-, $-C(OR^{13})_2$ or $-C(R^{11})(OH)$-; R^{11} is hydrogen or C_{1-3} alkyl; R^{12} is hydrogen, R^{14} (wherein R^{14} is alkyl moiety of chemically or physiologically hydrolyzable alkyl ester)
or M (wherein M is $NHR^{17}R^{18}R^{19}$ (wherein R^{17}, R^{18} and R^{19} are independently hydrogen or C_{1-4} alkyl), sodium, potassium or 1/2 calcium); two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $-(CH_2)_2$- or $-(CH_2)_3$- ; and R^{15} and R^{16} are independently hydrogen or
C_{1-3} alkyl; or R^{15} and R^{15} together form $-(CH_2)_2$- or $-(CH_2)_3$-).

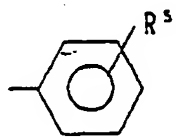
2. The compound according to Claim 1, wherein in the formula I, R^1 is hydrogen, C_{1-8} alkyl, C_2-6 alkenyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, fluoro, chloro, bromo,



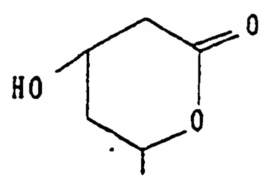
(wherein R^5, R^6 and R^7 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro or bromo), 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, 2- or 5-pyrimidyl or



(wherein R^5 is as defined above), or C_{1-3} alkyl substituted by

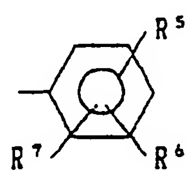


(wherein R^5 is as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-8} alkyl, or α-or β-naphthyl; R^2 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl; R^3 and R^4 are independently hydrogen, C_{1-8} alkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, t-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $-O(CH_2)_\ell OR^{10}$ (wherein R^{10} is hydrogen, or C_{1-3} alkyl, and ℓ is 1, 2 or 3); or when located at the ortho position to each other, R^3 and R^4 may together form methylenedioxy; Y is $-CH_2CH_2-$ or $-CH=CH-$; and Z is $-Q-CH_2WCH_2-CO_2R^{12}$,

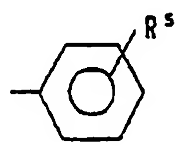


(wherein Q is -C(O)- or -CH(OH)-; W is -C(O)- or -C(OH)-; and R^{12} is as defined in Claim 1).

3. The compound according to Claim 1, wherein in the formula I, R^1 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl,



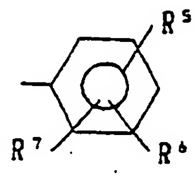
(wherein R^5, R^6 and R^7 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro or bromo), 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, or 2- or 5-pyrimidyl; or C_{1-3} alkyl substituted by



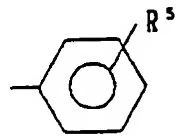
(wherein R^5 is as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-8} alkyl, or α-or β-naphthyl; R^2 is primary or secondary C_{1-4} alkyl or C_{3-6} cycloalkyl; R^3 and R^4 are as

defined in Claim 2 and located at the 3- and 4-position; Y is $-CH_2CH_2-$ or (E)-CH = CH-; and Z is as defined in Claim 2.

4. The compound according to Claim 1, wherein in the formula I, R^1 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl,



(wherein R^5, R^6 and R^7 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro or bromo); or C_{1-3} alkyl substituted by



(wherein R^5 ia as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-8} alkyl; R^2 is ethyl, n-propyl, i-propyl or cyclopropyl; R^3 and R^4 are independently hydrogen, C_{1-8} alkyl, fluoro, chloro or bromo, and they are located at the 3- and 4-position; and Y and Z are as defined in Claim 3.

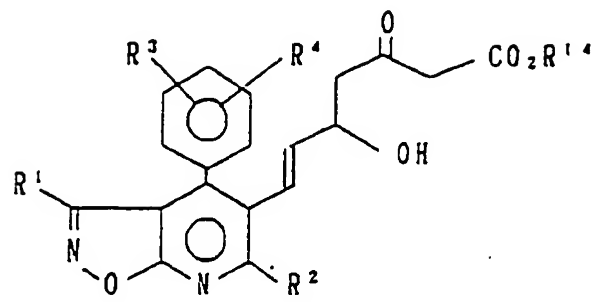
5. The compound according to Claim 1, wherein in the formula I, R^1 is hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, i-butyl, t-butyl, n-hexyl, n-octyl, vinyl, isopropenyl, cyclopropyl, cyclohexyl, phenyl, 2-toluyl, 3-toluyl, 4-toluyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethylphenyl, 3,4-dimethoxyphenyl, benzyl, α-methylbenzyl, 4-chlorobenzyl or 4-methoxybenzyl; R^2 is i-propyl or cyclopropyl; when R^4 is hydrogen, R^3 is hydrogen, 3-methyl, 4-methyl, 3-chloro, 4-chloro, 3-fluoro or 4-fluoro; or R^3 and R^4 together form 3-methyl-4-chloro, 3,5-dichloro, 3,5-difluoro, 3,5-dimethyl or 3-methyl-4-fluoro; and Y and Z are as defined in Claim 3.

6. The compound according to Claim 1, wherein in the formula I, R^1, R^3, Y and Z are as defined in Claim 1, and R^2 is cyclopropyl.

7. The compound according to Claim 1, which is (E)-7-[4′-(4″-fluorophenyl)-3′-methyl-6′-(1″-methylethyl)isoxazolo[5,4-b]pyridin-5′-yl]-3,5-dihydroxyhept-6-enoic acid, a sodium salt, methyl ester, ethyl ester, n-propyl ester or i-propyl ester of the carboxylic acid, or a lactone formed by the condensation of the carboxylic acid with hydroxy at the 5-position.

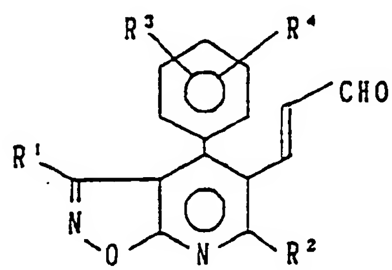
8. The compound according to Claim 1, which is (E)-7-[4′-(4″-fluorophenyl)-6′-(1″-methylethyl)-3′phenylisoxazolo[5,4-b]pyridin-5′-yl]-3,5-dihydroxyhept-6-enoic acid, a sodium salt, methyl ester, ethyl ester, n-propyl ester or i-propyl ester of the carboxylic acid, or a lactone formed by the condensation of the carboxylic acid with the hydroxy at the 5-position.

9. A process for producing a compound of the formula:



(II)

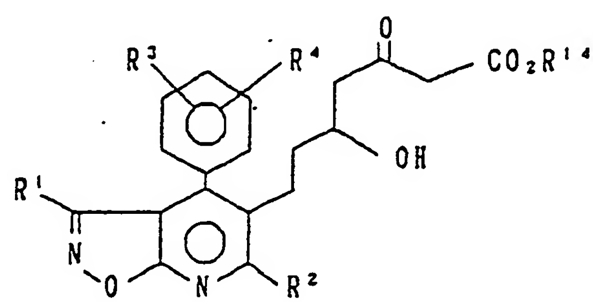
wherein R^1, R^2, R^3 and R^4 are as defined in Claim 1 and R^{14} is alkyl moiety of chemically or physiologically hydrolyzable alkyl ester, for example, C_{1-4} alkyl, which comprises reacting a compound of the formula:



(III)

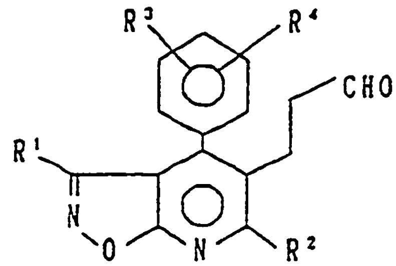
wherein R^1, R^2, R^3 and R^4 are as defined above, with a double anion of R^{14} ester of acetoacetic acid (wherein R^{14} is as defined above).

10. A process for producing a compound of the formula:



(XIV)

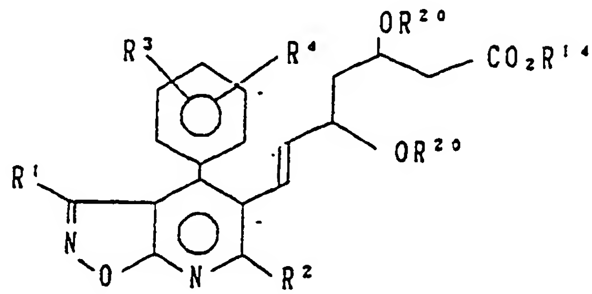
wherein R^1, R^2, R^3 and R^4 are as defined in Claim 1, and R^{14} is alkyl moiety of chemically or physiologically hydrolyzable alkyl ester, for example, C_{1-4} alkyl, which comprises reacting a compound of the formula:



(XIII)

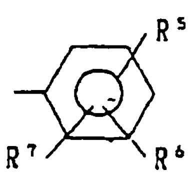
wherein R^1, R^2, R^3 and R^4 are as defined above, with a double anion of R^{14} ester of acetoacetic acid (wherein R^{14} is as defined above).

11. A process for producing a compound of the formula:

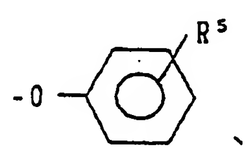


(XX)

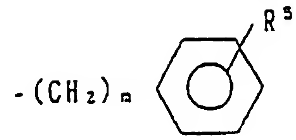
wherein R^1 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, fluoro, chloro, bromo,



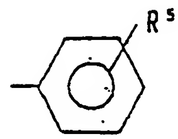
(wherein R^5, R^6 and R^7 are independently hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, C_{3-7} cycloalkyl, trifluoromethyl, fluoro, chloro, bromo), 2-, 3- or 4-pyridyl, 2- or 3- thienyl, 2- or 3-furyl, 2- or 5-pyrimidyl,



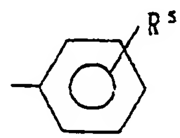
(wherein R^5 is as defined above), $-NR^8R^9$ (wherein R^8 and R^9 are independently C_{1-4} alkyl,



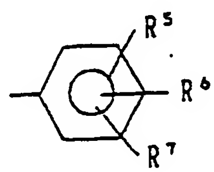
(wherein R^5 is as defined above, and m is 1, 2 or 3), or R^8 and R^8 together form $-(CH_2)_j-$ (wherein j is 3, 4 or 5)); or C_{1-3} alkyl substituted by



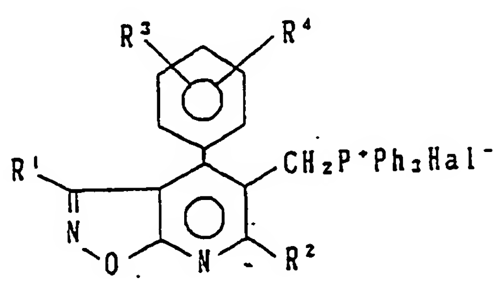
(wherein R^5 is as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-8} alkyl, or α-or β-naphthyl; R^2 is hydrogen, C_{1-8} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl or



(wherein R^5 is as defined above), or C_{1-3} alkyl substituted by one member selected from the group consisting of



(wherein R^5, R^6 and R^7 are as defined above) and by 0, 1 or 2 members selected from the group consisting of C_{1-3} alkyl; R^3 and R^4 are independently hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, $R^{23}R^{24}N$- (wherein R^{23} and R^{24} are independently C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, trimethylsilyloxy, diphenyl-t-butyl-silyloxy or $-O(CH_2)_\ell OR^{10}$ (wherein R^{10} is C_{1-3} alkyl, and ℓ is 1, 2 or 3); or when located at the ortho position to each other, R^3 and R^4 may together form -CH=CH-CH=CH- or methylenedioxy; R^{20} is a protecting group for hydroxyl; and R^{14} is alkyl moiety of chemically or physiologically hydrolyzable alkyl ester, for example, C_{1-4} alkyl; which comprises reacting the compound of the formula:



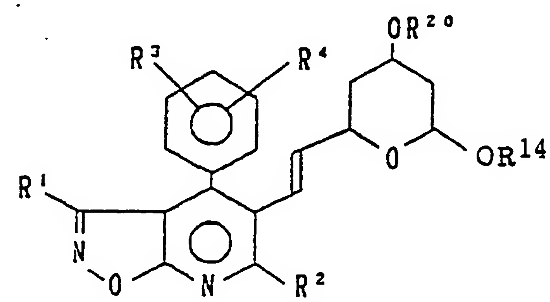
(XVIII)

wherein R^1, R^2, R^3 and R^4 ar as d fined above, and Hal is chlorin , bromin or iodin , with a strong alkali to form an ylide compound, and r acting th ylid with a compound of th formula:

$$\begin{array}{l} H(O)C\underset{|}{C}H(OR^{20}) \\ \quad\quad\; CH_2CH(OR^{20})CH_2CO_2R^{14} \end{array} \qquad (XIX)$$

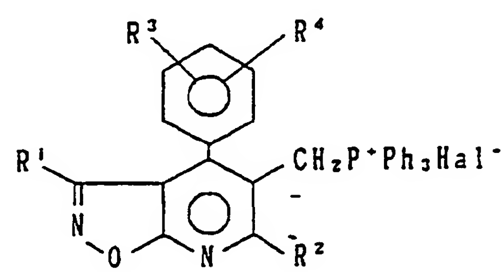
wherein R^{20} and R^{14} are as defined above.

12. A process for producing a compound of the formula:



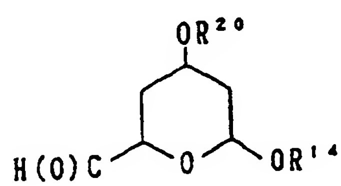
(XXII)

wherein R^1, R^2, R^3 and R^4 are as defined in Claim 11, R^{20} is a protecting group for hydroxyl, and R^{14} is alkyl moiety of chemically or physiologically hydrolyzable acetal, for example, C_{1-4} alkyl, which comprises reacting a compound of the formula:



(XVIII)

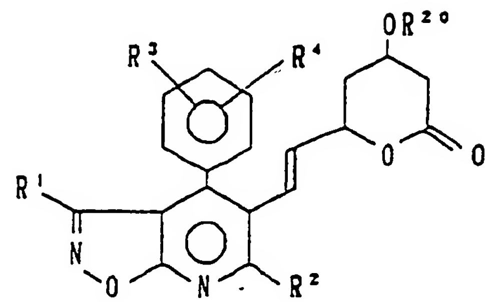
wherein R^1, R^2, R^3 and R^4 are as defined above, and Hal is as defined in Claim 11, with a strong alkali to form an ylide compound, and reacting the ylide with a compound of the formula:



(XXI)

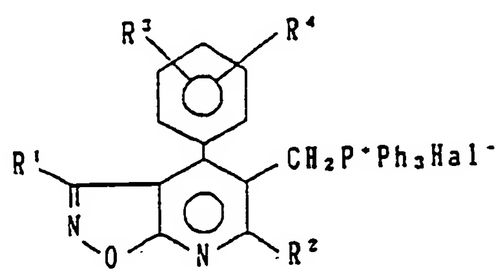
wherein R^{20} and R^{14} are as defined above.

13. A process for producing a compound of the formula:



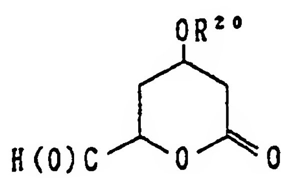
(XXIV)

wherein R^1, R^2, R^3 and R^4 are as defined in Claim 11; and R^{20} is a protecting group for hydroxyl, which comprises reacting a compound of the formula:



(XVIII)

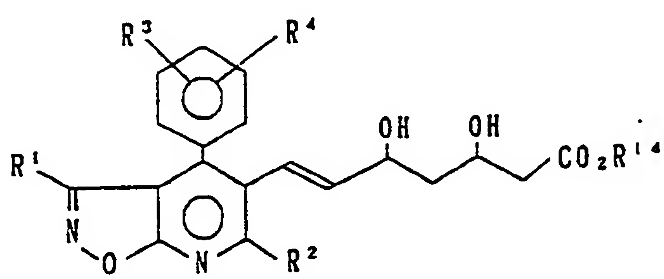
wherein R^1, R^2, R^3 and R^4 are as defined above, and Hal is as defined in Claim 11, with a strong alkali to form an ylide compound, and reacting the ylide with a compound of the formula:



(XXIII)

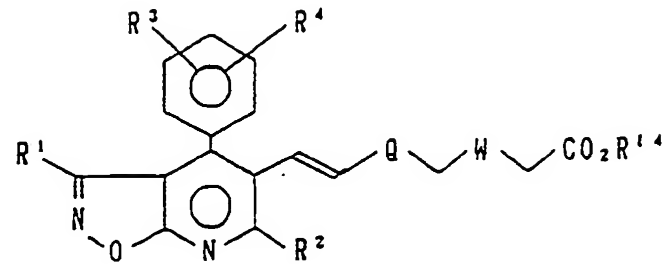
wherein R^{20} is a protecting group for hydroxyl.

14. A process for producing a compound of the formula:



(I-1)

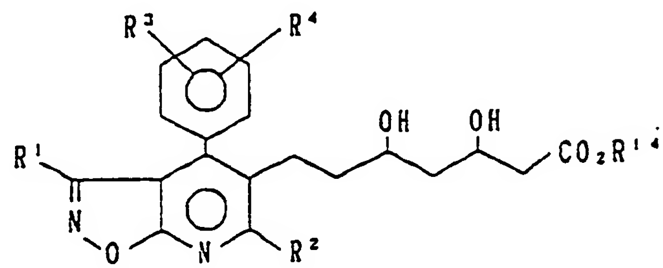
wherein R^1, R^2, R^3 and R^4 are as defined in Claim 1, and R^{14} is alkyl moiety of chemically or physiologically hydrolyzable alkyl ester, which comprises reducing a compound of the formula:



	Q	W
(II)	-CH(OH)- ,	-C(O)-
(I-6)	-C(O)- ,	-CH(OH)-
(XV)	-C(O)- ,	-C(O)-

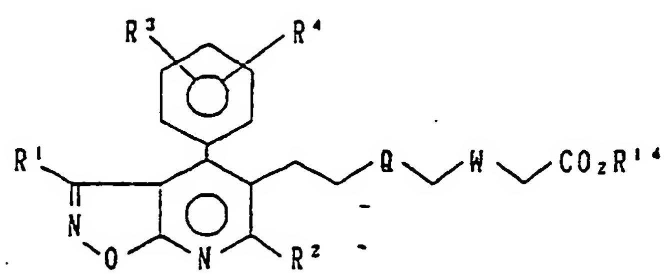
wherein R^1, R^2, R^3, R^4 and R^{14} are as defined above, by a reducing agent.

15. A process for producing a compound of the formula:



(I-7)

wherein R^1, R^2, R^3 and R^4 are as defined in Claim 1, and R^{14} is alkyl moiety of chemically or physiologically hydrolyzable alkyl ester, for example, C_{1-4} alkyl, which comprises reducing a compound of the formula:



	Q	W
(XIV)	-CH(OH)- ,	-C(O)-
(XVI)	-C(O)- ,	-CH(OH)-
(XVII)	-C(O)- ,	-C(O)-

wherein R^1, R^2, R^3, R^4 and R^{14} are as defined above, by a reducing agent.

16. An anti-hyperlipidemia agent containing the compound of the formula I as defined in Claim 1.

17. An anti-hyperlipoproteinemia agent containing the compound of the formula I as defined in Claim 1.

18. An anti-atherosclerosis agent containing the compound of the formula I as defined in Claim 1.

19. A method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the compound of the formula I as defined in Claim 1.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Pat nt Conventi n shall be c nsider d, for the purposes of subsequent proceedings, as the European search report

Application number

EP 89120770.6

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)5
A	DE - A - 1 695 931 (THE UPJOHN CO.) * Claim; pages 1,7 *	1-5	C 07 D 498/04 A 61 K 31/42 A 61 K 31/44// (C 07 D 498/04, C 07 D 261:00, C 07 D 221:00)
A	DE - A - 1 695 933 (THE UPJOHN CO.) * Claim 1; page 3 *	1-5	
A	DE - A1 - 3 447 388 (GÖDECKE AG) * Claim 1 *	1-5,18	
D,A	EP - A2 - 0 244 364 (SANDOZ-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H.) * Pages 1,3,4,7,9,10,11,13, 14,16,17 *	1,9-18	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)5

C 07 D 498/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-18

Claims searched incompletely: -

Claims not searched: 19

Reason for the limitation of the search:

Method for treatment of the human or animal body by therapy (Art. 52(4) EPC)

Place of search	Date of completion of the search	Examiner
VIENNA	12-02-1990	PETROUSEK

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
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